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RESEARCH**

APPLICATION NUMBER:

217686Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	217686
Priority or standard	STANDARD
Submit date(s)	12/19/2022
Received date(s)	12/19/2022
PDUFA goal date	3/19/2024
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	3/14/2024
Established/proper name	aprocitentan
(Proposed) proprietary name	TRYVIO
Pharmacologic class	Endothelin receptor antagonist
Other product name(s)	Click or tap to enter name.
Applicant	IDORSIA PHARMACEUTICALS LTD
Dosage form(s)/formulation(s)	TABLET
Dosing regimen	12.5 mg once daily, (b) (4)
Applicant-proposed indication(s)/ population(s)	Aprocitentan, in combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs
SNOMED CT code for proposed indication disease term(s)¹	38341003 (Hypertensive disorder, systemic arterial (disorder))
Regulatory action	Approval
Approved dosage (if applicable)	12.5 mg once daily
Approved indication(s)/ population(s) (if applicable)	TRYVIO, in combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure (BP) in patients who are not adequately controlled on other drugs
SNOMED CT code for approved indication disease term(s)¹	38341003 (Hypertensive disorder, systemic arterial (disorder))

¹ For internal tracking purposes only.

Abbreviations: BP, blood pressure; DCN, Division of Cardiology and Nephrology; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AOBPM	automated office blood pressure measurement
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
BSEP	bile salt export pump
CAC	central adjudication committee
CDER	Center for Drug Evaluation and Research
CHO	Chinese hamster ovary
CI	confidence interval
CKD	chronic kidney disease
CL	total body clearance of drug
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRO	clinical research organization
CYP	cytochrome p450 enzyme
DB	double-blind
DBP	diastolic blood pressure
DCN	Division of Cardiology and Nephrology
DOCA	deoxycorticosterone acetate
DRF	dose range-finding
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EFD	embryo-fetal development
E-R	exposure-response
ERA	endothelin receptor antagonist
ET	endothelin
ET_A	endothelin receptor A
ETASU	elements to assure safe use
ET_B	endothelin receptor B
FAS	full analysis set
FDA	U. S. Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FRP	female adults of reproductive potential

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GD	gestational day
GLP	good laboratory practice
HI	hepatic impairment
HSD	high sodium diet
IC ₅₀	half maximal inhibitory concentration
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IND	investigational new drug
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of quantification
LSM	least square mean
MACE	major adverse cardiovascular events
MAP	mean arterial pressure
MAR	missing at random
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate
NDA	new drug application
NMT	not more than
NOAEL	no observed adverse effect level
NTCP	sodium-dependent taurocholate co-transporting polypeptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PAH	pulmonary arterial hypertension
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
PO	oral/by mouth
PopPK	population pharmacokinetic
PPND	pre- and postnatal development
PXR	human pregnane X receptor
QT	QT interval
REMS	risk evaluation and mitigation strategy
RHT	resistant hypertension
RI	run-in
RSE	relative standard error
SAE	serious adverse event

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SAP	statistical analysis plan
SB	single-blind
SBAT	standard background antihypertensive therapy
SBP	systolic blood pressure
SHR	spontaneously hypertensive
SiDBP	sitting diastolic blood pressure
SiSBP	sitting systolic blood pressure
SUSAR	serious, unexpected, and suspected adverse reaction
TEAE	treatment-emergent adverse event
T _{max}	time to maximum concentration
UACR	urine albumin-to-creatinine ratio
uAOBPM	unattended automated office blood pressure measurement
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
WD	withdrawal

I. Executive Summary

1. Summary of Regulatory Action

On December 19, 2022, Idorsia Pharmaceuticals Ltd. submitted an original NDA for aprocitentan for the following indication: “Aprocitentan, in combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure in patients who are not adequately controlled on other drugs.”

Aprocitentan is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin (ET)-1 to ET_A and ET_B receptors. ET-1, via its receptors (ET_A and ET_B), mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. ET-1 has been implicated in the pathogenesis of hypertension, including mediation of endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis. Of note, aprocitentan has the same chemical structure as the active metabolite of macitentan, which is approved for the treatment of pulmonary arterial hypertension.

In support of the proposed indication, the Applicant submitted the results of an adequate and well-controlled multipart, Phase 3 study (PRECISION) in adults with a systolic blood pressure ≥ 140 mmHg who were prescribed at least three antihypertensive medications. The study included a 4-week double-blind, placebo-controlled treatment period in which 730 subjects were randomized 1:1:1 to aprocitentan 12.5 mg, 25 mg, or placebo once daily (Part 1), a 32-week period in which all subjects were treated with aprocitentan 25 mg (Part 2), and another double-blind period in which subjects were rerandomized to receive either aprocitentan 25 mg or placebo (randomized withdrawal/Part 3).

The review team has concluded that the application provides substantial evidence of aprocitentan’s effectiveness in reducing blood pressure when used in combination with other antihypertensive drugs in subjects who are not adequately controlled on other drugs. Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality. Hence, the Agency accepts blood pressure lowering as a validated surrogate endpoint and basis for traditional approval of antihypertensive agents. The product’s efficacy in lowering blood pressure was demonstrated in both the initial double-blind treatment period as well as in the randomized withdrawal period of the Phase 3 study. As such, the study is considered to be the scientific equivalent of two clinical investigations.

As previously noted, aprocitentan has the same chemical structure as the active metabolite of macitentan and the results of safety analyses were as a whole consistent with risks that might be expected given the known risks of macitentan and other endothelin receptor antagonists. Because of the risk of embryo-fetal toxicity, aprocitentan will only be available through a restricted distribution program under a risk evaluation and mitigation strategy (REMS).

The Applicant has proposed use as an add-on therapy in patients with uncontrolled hypertension and given the product’s safety profile, aprocitentan will not be approved as initial (first-line)

NDA 217686
TRYVIO (aprocitentan)

therapy for the treatment of hypertension in adults. Although it is acknowledged that other members of the endothelin receptor antagonist class are indicated as first-line therapy for other diseases (e.g., IgA nephropathy, pulmonary arterial hypertension), the benefit risk considerations are different for essential hypertension for which there are multiple other therapeutic options with better safety profiles.

(b) (4) the Applicant evaluated two doses in their Phase 3 study, (b) (4)
(b) (4) the 12.5 mg dose will be approved (b) (4). A shallow exposure-response profile was observed in the overall population. However, variability was observed suggesting that if the Applicant could identify intrinsic factor(s) that predict lower exposure it may be possible to identify a subpopulation of patients that might benefit from increasing the dose from 12.5 mg to 25 mg.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• The prevalence of hypertension in the United States is high, and nearly half of adults in the United States (approximately 48%) have a systolic blood pressure >130 mmHg, diastolic blood pressure >80 mmHg, or are taking a medication for hypertension. Hypertension is associated with an increased risk of cardiovascular disease, stroke, and end-stage kidney disease. • A continuous association exists between higher blood pressure and increased cardiovascular disease risk, and even modest reductions of severe hypertension can provide substantial benefit. • Hypertension that is difficult-to-control is often characterized as “uncontrolled” (i.e., blood pressure above goal) or “resistant” hypertension. Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes (including a diuretic) at maximum recommended (or maximally tolerated) doses. The prevalence of true resistant hypertension is not known, and many patients who meet the definition of resistant hypertension have been found to have poor adherence or inadequate treatment regimens.	Hypertension is common in the United States and is a serious disease associated with significant morbidity and mortality. Patients with uncontrolled hypertension are at high risk for cardiovascular events.
Current treatment options	• Numerous antihypertensive drugs from a variety of pharmacologic classes and with different mechanisms of action are available and have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality. From these trials, it can be concluded that it is the blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. • Many patients will require more than one drug from different pharmacological classes to achieve blood pressure goals. Patients with difficult-to-control hypertension often need several drugs (e.g., ≥3) from different pharmacological classes to achieve blood pressure goals.	Many patients will require more than one drug from different pharmacological classes to achieve blood pressure goals. Despite the availability of several classes of antihypertensive therapies, many patients remain uncontrolled.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	- The efficacy of aprocitentan was evaluated in a multipart, Phase 3 multicenter study (PRECISION) in adults with SBP $\geq$140 mmHg who were prescribed at least three antihypertensive medications. The study evaluated the effect of aprocitentan 12.5 mg and 25 mg on blood pressure. The study included a 4-week double-blind, placebo-controlled treatment period (Part 1), 32-week single-blind treatment period (Part 2), and a 12-week placebo-controlled, double-blind withdrawal period (Part 3). The primary efficacy endpoint was the change from baseline to Week 4 of double-blind treatment in mean trough SiSBP, recorded via uAOBPM. The key secondary endpoint was the change from double-blind-withdrawal baseline (Week 36) to Week 40 in mean trough SiSBP, recorded via uAOBPM. - In the PRECISION study, both the 12.5 mg and 25 mg doses met the primary endpoint. The LSM difference (97.5% CI) in SiSBP at Week 4 compared to baseline was -15.4 mmHg (-17.5, -13.3) for aprocitentan 12.5 mg, -15.2 mmHg (-17.3, -13.2) for aprocitentan 25 mg, and -11.6 mmHg (-13.7, -9.5) for placebo¹, for a difference versus placebo of -3.8 mmHg (-6.8, -0.8; p-value=0.0043) and -3.7 mmHg (-6.6, -0.7; p-value=0.0054), respectively. - The PRECISION study also met the key secondary endpoint, demonstrating the persistence of aprocitentan's BP lowering effect. The LSM difference in blood pressure at Week 40 compared to Week 36 for aprocitentan 25 mg compared to placebo was -5.7 mmHg (95%CI: -7.8, -3.6; p-value<0.0001). - Aprocitentan's blood pressure lowering effect appeared consistent among subgroups defined by age, sex, race, BMI, baseline eGFR, baseline UACR, and medical history of diabetes. (b) (4)	The submitted data provide substantial evidence of aprocitentan's effectiveness in lowering blood pressure when administered in combination with other antihypertensive medications in patients who are not adequately controlled on other drugs. Data from Part 1 of the PRECISION study indicate that in the study population as a whole, the 12.5 mg and 25 mg doses of aprocitentan provided similar efficacy and (b) (4) the 12.5 mg dose will be approved.
Risk and risk management	Risks of aprocitentan in PRECISION were generally consistent with the known risks of endothelin receptor antagonists.	The results of safety analyses were as a whole consistent with risks that might be expected

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	– Anemia is a known risk of endothelin receptor antagonists and is thought to be due in part to hemodilution. In the initial 4-week double-blind treatment period, the incidence of a hemoglobin decrease >2 g/dL compared to baseline was greater in subjects receiving aprocitentan (7% and 3% in the aprocitentan 12.5 mg and 25 mg arms, respectively) compared to subjects treated with placebo (1%). Hemoglobin decreases usually presented early, stabilized thereafter, and were reversible after discontinuation. – Fluid retention is a known risk of endothelin receptor antagonists. In Part 1, fluid retention was reported in 9% of subjects receiving aprocitentan 12.5 mg as compared with 18% of subjects receiving aprocitentan 25 mg and 2% on placebo. The majority of edema events were reported as mild to moderate in severity and did not lead to treatment discontinuation. – Endothelin receptor antagonists can cause hepatotoxicity, though the degree of risk varies amongst members of the class. In PRECISION, there were two subjects with liver enzyme elevations of greater than 5-fold the upper limit of normal which were assessed as highly likely related to the use of aprocitentan. Both subjects had positive rechallenges. There were no cases of ALT and/or AST >3 × ULN and total bilirubin >2 × ULN or liver failure. • Based on data from animal reproduction studies with endothelin receptor antagonists, aprocitentan can cause fetal harm when administered during pregnancy. • Based on data from other endothelin receptor antagonists, aprocitentan may have an adverse effect on spermatogenesis. • Hypersensitivity related-AEs were reported in 0.8% of subjects taking aprocitentan 12.5 mg and 0.4% of subjects taking 25 mg compared with no patients receiving placebo in Part. During Part 2, one subject taking 25 mg had an SAE of allergic dermatitis requiring hospitalization and experienced recurrence of the allergic dermatitis with rechallenge.	given the known risks of macitentan and other endothelin receptor antagonists. Because of the risk of embryo-fetal toxicity, aprocitentan will only be available through a restricted distribution program under a REMS. Some endothelin receptor antagonists can cause severe liver injury, including liver failure. Although the available data indicate that aprocitentan can cause liver injury, the injuries seen in the aprocitentan clinical trials were modest and reversible. Given these findings, as well as the existing risk mitigation for macitentan (aprocitentan is a metabolite of macitentan), labeling is considered adequate to mitigate this risk, similar to macitentan. Postmarketing surveillance will include enhanced pharmacovigilance for liver injury to assess for serious events occurring in the postmarketing setting. Labeling will contraindicate use in pregnancy and in patients who are hypersensitive to aprocitentan or any of its excipients. Given the safety findings in the development program and larger experience with the pharmacologic class, labeling will also include Warnings and Precautions for embryo-fetal toxicity, hepatotoxicity, fluid retention, hemoglobin decrease, and decreased sperm counts.

¹ The primary objective of the PRECISION study was to demonstrate the blood pressure-lowering effect of aprocitentan when added to standard-of-care in subjects with “true” resistant hypertension. The substantial reduction in blood pressure seen in the placebo arm in Part 1 of the study indicates that while the study population had uncontrolled hypertension, it was not necessarily “true” resistant hypertension.

Abbreviations: AESIs, adverse events of special interest; ALT, alanine transaminase; AST, aspartate transferase, BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DB, double-blind; DB-WD, double-blind withdrawal; EFD, embryo-fetal development; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; ESKD, end-stage kidney disease; LSM, least squares mean; PMR, postmarketing requirement; REMS, REMS, risk evaluation and mitigation strategy; SBP, systolic blood pressure; SB, single-blind; SiSBP, sitting systolic blood pressure; uAOBPM, unattended automated office blood pressure measurement; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal

2.2. Conclusions Regarding Benefit-Risk

Aprocitentan at doses of 12.5 mg daily and 25 mg daily was demonstrated to lower blood pressure in patients taking other antihypertensive medications, and thus is expected to reduce the risk of cardiovascular events in these patients. Although two doses were studied in the Phase 3 trial, the 25 mg dose does not appear to provide a meaningful improvement in blood pressure reduction as compared to the 12.5 mg dose.

Based on data from animal reproduction studies with endothelin receptor antagonists, aprocitentan can cause embryo-fetal toxicity when administered during pregnancy and a REMS will be required to mitigate this risk by ensuring prescribers are educated about appropriate patient counseling (i.e., need for contraception and pregnancy testing). Although the available data indicate that aprocitentan can cause liver injury, the injuries seen in the aprocitentan clinical trials were modest and reversible. Similar to macitentan, hepatotoxicity will be included as a labeled risk for aprocitentan, and periodic liver tests will be recommended. Other risks (i.e., fluid retention, hemoglobin decrease, and decreased sperm counts) will also be described as Warnings in the label. To mitigate the risks of fluid retention and hemoglobin decrease, the label will also include periodic monitoring for signs and symptoms of fluid retention, weight gain, and worsening heart failure, and periodic assessments of hemoglobin, respectively.

Given the measures that will be put in place, aprocitentan's benefits outweigh its risks. Because of aprocitentan's safety profile, as well as the availability of other antihypertensive agents with more benign safety profiles, the benefit-risk profile is considered favorable only when used in combination with other agents to lower blood pressure in patients who are not adequately controlled on other drugs (i.e., not as first-line therapy).¹ For these patients, the clinical benefit of reducing cardiovascular risk outweighs risks that are either manageable (fluid retention, hemoglobin reduction, liver injury) or have rigorous risk mitigation requirements (embryofetal toxicity).

(b) (4)

the 12.5 mg dose will be approved.

¹ Although we acknowledge members of the endothelin receptor antagonist class are indicated as first-line therapy for other diseases (e.g., pulmonary arterial hypertension), the benefit risk considerations are different for essential hypertension for which there are multiple other therapeutic options with more reassuring safety profiles.

II. Interdisciplinary Assessment

3. Introduction

Aprocitentan is an orally active, dual endothelin-receptor antagonist (ERA) that inhibits the binding of endothelin (ET)-1 to ET receptors A and B (ET_A and ET_B). ET-1, via its receptors (ET_A and ET_B), mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation and inflammation. ET-1 upregulation and can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation and increased aldosterone synthesis, and thus, contributes to blood pressure elevation. Aprocitentan has the same chemical structure as the active metabolite of macitentan. Macitentan is approved for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH.

On December 19, 2022, the Applicant submitted an NDA for aprocitentan for the treatment of hypertension to lower blood pressure under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Disease Background

The prevalence of hypertension in the United States is high,² and nearly half of adults in the United States (approximately 48%) have a systolic blood pressure >130 mmHg, diastolic blood pressure >80 mmHg, or are taking a medication for hypertension ([Centers for Disease Control and Prevention 2023](#)). In the United States, the prevalence of hypertension is higher among males, older adults, Black adults, and those with obesity, chronic kidney disease, or diabetes ([Ostchega et al. 2020](#)). Hypertension is associated with an increased risk of cardiovascular disease, stroke, and end-stage kidney disease. In 2010, in the United States, hypertension accounted for more cardiovascular deaths than any other modifiable cardiovascular disease risk factor and was second to cigarette smoking as a preventable cause of death for any reason ([Whelton et al. 2018](#)). A continuous association exists between higher blood pressure and increased cardiovascular disease risk, and even modest reductions of severe hypertension can provide substantial benefit.

Treatment of hypertension is among the most common reasons for healthcare office visits and for the use of chronic prescription medications. Control of high blood pressure with medication is part of comprehensive cardiovascular risk management (e.g., lipid control, smoking cessation, exercise, and limited sodium intake). Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action are available and have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality. From these trials, it can be concluded that it is the blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest

² The exact prevalence of hypertension depends upon the definition of hypertension and varies according to the guideline/threshold used. Per the National Health and Nutrition Examination Survey (NHANES) conducted between 2017-2018, in the United States, approximately 45% of U.S. adults met the definition of hypertension per the 2017 ACC/AHA guideline (i.e., BP >130/80 mmHg).

and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly. Many patients will require more than one drug from different pharmacological classes to achieve blood pressure goals. Primary agents for the treatment of high blood pressure include thiazide diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers. Secondary agents include loop diuretics, potassium-sparing diuretics, aldosterone antagonists, beta-blockers, direct renin inhibitors, alpha-1 blockers, and centrally acting drugs, and direct vasodilators ([Whelton et al. 2018](#)).

Hypertension that is difficult-to-control is often characterized as “uncontrolled” (i.e., blood pressure above goal) or “resistant” hypertension. Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes at maximum recommended (or maximally tolerated) doses. If tolerated, one of the three agents should be a diuretic. Patients whose blood pressure is controlled with four or more medications are also considered to have resistant hypertension. “True” resistant hypertension is distinguished from “apparent resistant” and pseudoresistant hypertension through 24-hour ambulatory blood pressure monitoring and lack of attribution to other factors (e.g., poor adherence to antihypertensive therapy, white coat hypertension, poor adherence to dietary and lifestyle approaches, suboptimal antihypertensive therapy, and inaccurate measurement of blood pressure). The prevalence of true resistant hypertension is not known, and many patients who meet the definition of resistant hypertension have been found to have poor adherence or inadequate treatment regimens. Data from the National Health and Nutrition Examination Survey from 2003 through 2008 in nonpregnant US adults with hypertension showed that approximately 9% met criteria for apparent resistant hypertension. Adults with resistant hypertension were more likely to be older, non-Hispanic black, have higher body mass index, albuminuria, reduced renal function, and self-reported medical histories of coronary heart disease, heart failure, stroke, and diabetes mellitus ([Persell 2011](#)).

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Dosing Recommendations: (b) (4)

3.1.2. Key Safety Review Issues

3.1.2.1. Hepatotoxicity

3.1.2.2. Embryo-Fetal Toxicity

3.2. Approach to the Clinical Review

This review focused on the efficacy and safety findings in Study ID-080A301, referred to as PRECISION ([Table 3](#)).

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for Aprocitentan

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Dosing Regimen	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
ID-080A301 (PRECISION)	Adults with SBP ≥140 mmHg who were prescribed at least 3 antihypertensive medications	4-week placebo run-in period; 4-week DB, randomized, PC treatment period (Part 1); 32-week SB treatment period (Part 2); 12-week randomized, PC, DB-WD period (Part 3)	Drug: Aprocitentan or placebo Dosage: 12.5 mg (Part 1) or 25 mg (Parts 1, 2, 3)	<u>Primary:</u> change in sitting SBP from baseline to Week 4 during Part 1, measured at trough by uAOBPM <u>Key Secondary:</u> change in sitting SBP measured at trough by uAOBPM from Week 36 to Week 40	Planned: 600 Actual: 730 randomized equally to either placebo, aprocitentan 12.5 mg, or aprocitentan 25 mg during Part 1	138 sites, 20 countries

Source: Reviewer.

Abbreviations: DB, double-blind; DB-WD, double-blind withdrawal; PC, placebo-controlled; SB, single-blind; SBP, systolic blood pressure; uAOBPM, unattended automated office blood pressure measurement

4. Patient Experience Data

Table 4. 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	
☐	Observer-reported outcome	
☐	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

5.1.1. Primary Pharmacology

ET-1 mediates a variety of deleterious effects via activation of its receptors (ET_A and ET_B), such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. Aprocitentan is an ERA that potently inhibits the binding of ET-1 to ET_A and ET_B receptors. Aprocitentan showed receptor inhibitor behavior both in vitro and in vivo, with a consistent preferential inhibition for ET_A versus ET_B receptors noted across studies.

- The inhibitory effect of aprocitentan on receptor function was assessed using microsomal membranes from Chinese hamster ovary (CHO)-K1 cells expressing recombinant human ET_A or ET_B receptors. In this assay, aprocitentan inhibited ¹²⁵I-ET-1 binding to human recombinant ET_A and ET_B receptors with half maximal inhibitory concentration values of 3.4±0.4 nM and 987±185 nM, respectively. Therefore, inhibition of ET_A was approximately 290-fold more potent than for ET_B in this cell-free study.
- In recombinant cells, aprocitentan inhibited the ET-1-induced increase in cytosolic Ca²⁺ (a measure of downstream ET-1 signaling) with a geometric mean Schild Kb inhibitor potency value of 5.5 nM and 319 nM on ET_A and ET_B receptors, respectively, where Kb is the inhibition constant of the binding of the antagonist to the receptor. Thus, inhibition was approximately 60-fold more potent for ET_A than ET_B in intact cells.
- Aprocitentan inhibited ET-1-induced contraction (ET_A-mediated) in endothelium denuded rat aorta and sarafotoxin S6c-induced contraction (ET_B-mediated) in epithelium denuded rat trachea with pA₂ values of 6.7±0.2 and 5.5±0.3, respectively. The pA₂ value represents negative logarithm of the molar concentration of an antagonist that produces a 2-fold shift in the concentration response curve. These data demonstrated functional inhibitory activity of aprocitentan on ET_A or ET_B in isolated tissues.
- Given the difference in potency between ET_A and ET_B observed in vitro, a study was conducted to establish the inhibitory effect of aprocitentan on the ET_B receptor in vivo, which is reported to be involved in the clearance of ET-1 from the plasma ([Loffler et al. 1993](#); [Fukuroda et al. 1994](#)). ([Loffler et al. 1993](#); [Fukuroda et al. 1994](#)). Aprocitentan treatment in normotensive rats resulted in a dose-dependent increase in plasma ET-1 demonstrating its inhibitory effect on ET_B in vivo. These data indicate that while a greater potency for ET_A versus ET_B exists, as demonstrated in vitro, aprocitentan can also inhibit the ET_B receptor in vivo.

5.1.2. Animal Model Data Showing Proof of Concept for Efficacy

Proof of concept supporting the efficacy of aprocitentan for the proposed indication was demonstrated in various animal models including deoxycorticosterone acetate (DOCA)-salt rats in which hypertension is induced by unilateral nephrectomy, mineralocorticoid analog DOCA pellet implantation and exposure to dietary salt (1% NaCl in drinking water); Dahl-S rats in which hypertension is induced by increased dietary salt (1% NaCl in drinking water); spontaneously hypertensive (SHR) rats in which hypertension is mediated through the renin angiotensin system and sympathetic nervous system.

Acute administration of aprocitentan resulted in a dose-dependent decrease in blood pressure (BP) without any effect on heart rate in all three animal models, demonstrating an antihypertensive effect. At a dose of 100 mg/kg, aprocitentan decreased mean arterial pressure more effectively in Dahl-S (↓36 mmHg) and DOCA-salt (↓29 mmHg) rats than in SHR (↓18 mmHg), indicating that activation of the ET system was more prominent in salt-sensitive and volume-dependent hypertensive models (DOCA-salt and Dahl-S models) compared to the essential hypertension model (SHR rats).

The protective effect of aprocitentan on heart and kidney function was evaluated in DOCA-salt rats following a 4-week treatment period. In DOCA-salt rats, aprocitentan dose-dependently attenuated mean arterial pressure (without affecting heart rate), increased renal blood flow, decreased renal vascular resistance, and reduced elevated plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. However, treatment did not fully ameliorate the cardiac (cardiomyopathic condition) and kidney (minimal to marked hydronephrosis, tubulonephrosis, interstitial nephritis and glomerular changes) findings. The results of this study suggest that aprocitentan treatment may partially improve cardiac and renal function in a hypertensive rat model.

Treatment with aprocitentan in combination with other standard antihypertensive therapies was also evaluated in DOCA-salt rats and SHR rats. Aprocitentan, compared with spironolactone, was tested in combination with other standard antihypertensive therapies (e.g., valsartan, enalapril and amlodipine). The aprocitentan/valsartan combination demonstrated synergistic effect in DOCA-salt and SHR rats whereas the spironolactone/valsartan combination only produced additive effects in these models. The aprocitentan/enalapril combination demonstrated synergistic effect in SHR rats and an additive effect in DOCA-salt rats. The aprocitentan/amlodipine combination showed only additive effects in both rat models. These results suggested that aprocitentan treatment may have an additive or synergistic effect on BP reduction when coadministered with other antihypertensive drugs.

5.2. Clinical Pharmacology/Pharmacokinetics

- No dose adjustment is required in patients with mild or moderate hepatic impairment. Aprocitentan has not been studied in patients with severe hepatic impairment (Section [8.1](#)).
- No dose adjustment is needed for patients with renal impairment; however, aprocitentan was not studied in patients with eGFR <15 mL/min or in patients undergoing dialysis and is not recommended in these patients (Section [8.1](#)).
- Aprocitentan did not alter the pharmacokinetic (PK) profile of midazolam or 1-hydroxy midazolam to a clinically relevant extent (Section [8.2](#)).
- Aprocitentan did not alter the PK of rosuvastatin to a clinically relevant extent (Section [8.2](#)).
- Aprocitentan may be taken with or without food (Section [8.2](#)).
- Glucosidation of aprocitentan to M3 accounts for 25.2% of the administered dose (Section [8.2](#)).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information						
	<i>Pharmacologic Activity</i>						
Established pharmacologic class (EPC)	Endothelin receptor antagonist (ERA)						
Mechanism of action	Aprocitentan is an endothelin receptor antagonist that inhibits the binding of endothelin (ET) to ET _A and ET _B receptors						
Active moieties	Aprocitentan						
QT prolongation	A 100 mg dose (8 times the 12.5 mg therapeutic dose) did not show clinically significant corrected QT interval prolongation.						
	<i>General Information</i>						
Bioanalysis	The bioanalytical method for aprocitentan in plasma used liquid chromatography/mass spectrometry (LC-MS/MS) with protein precipitation extraction. The calibration range was 5 to 10,000 ng/mL. The method is acceptable.						
Healthy subjects versus hypertensive subjects	Mean predose concentrations of aprocitentan in the plasma of subjects with hypertension in the Phase 3 study (Study ID-0810A301) and healthy subjects from Phase 1 studies (AC-080-101, ID-080-102, ID-080-107, ID-080-108) after repeated administration were similar.						
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<table border="0"> <tr> <td>Parameter</td> <td>Geometric mean (%CV_{In})</td> </tr> <tr> <td>AUC_T</td> <td>72 µg□h/mL</td> </tr> <tr> <td>C_{max}</td> <td>3.7 µg/mL</td> </tr> </table> Parameters are from study ID-080-108 for a 25 mg dose	Parameter	Geometric mean (%CV _{In})	AUC _T	72 µg□h/mL	C _{max}	3.7 µg/mL
Parameter	Geometric mean (%CV _{In})						
AUC _T	72 µg□h/mL						
C _{max}	3.7 µg/mL						
Range of effective dose(s) or exposure	In the Phase 2 study (Study AC-080A201), aprocitentan 10, 25, and 50 mg decreased sitting systolic/diastolic unattended automated office BP from baseline to Week 8 (placebo-corrected decreases: 7.1/4.9, 9.9/7.0, and 7.6/5.0 mmHg, respectively). For hypertensive subjects with valid ambulatory BP, aprocitentan 10, 25, and 50 mg decreased placebo-corrected 24 h systolic/diastolic BP by 4.0/4.0, 4.8/5.9, and 3.7/4.5 mmHg, respectively. In the Phase 3 study (AC-080A301), aprocitentan 12.5 mg and 25 mg decreased sitting systolic/diastolic unattended automated office BP from baseline to Week 4 (placebo-corrected decreases: 3.8/3.9 and 3.7/4.5 mmHg, respectively). For hypertensive subjects with valid ambulatory BP, aprocitentan 12.5 mg and 25 mg decreased placebo-corrected 24 h systolic/diastolic BP by 4.2/4.3 and 5.9/5.8 mmHg, respectively.						
Maximally tolerated dose or exposure	A maximum tolerated dose was not established.						
Dose proportionality	Dose-proportional in the range of 5 to 100 mg following once daily multiple-dose administration						
Accumulation	At 25 mg, the accumulation index was approximately 3.						
Time to achieve steady-state	Approximately 8 days						
Bridge between to-be-marketed and clinical trial/study formulations	The formulation used in the Phase 3 study is comparable to the commercial formulation. The compositions are the same except for the film-coating color and debossing of the tablets.						

Characteristic	Drug Information
	Absorption
Bioavailability	Absolute bioavailability has not been determined in humans.
T _{max}	At steady-state for the 25 mg dose, the median T _{max} was 4 hours (range 1-10 hours)
Food effect (fed/fasted)	The food effect study was conducted with a high-fat, high-calorie meal
Geometric least square mean and 90% CI	Parameter: Ratio of Geometric Means 90% CI of the Ratio AUC _{0-∞} 1.23 1.07, 1.41 C _{max} 1.73 1.51, 1.98 T _{max} -1.0 (median of difference) -4.00, 1.50 (90% CI of the median)
	Distribution
Volume of distribution	19.3 L
Plasma protein binding	99.5% (in vitro)
Drug as substrate of transporters	Aprocitentan is a substrate of P-gp and BCRP in vitro. Inhibitors of these transporters are not expected to influence the PK of aprocitentan. Aprocitentan has a high permeability across cell membranes, so the cellular uptake is mainly driven by passive diffusion.
	Elimination
Mass balance results	Urine was the primary route of elimination. A total of 52% of drug material was eliminated in the urine, and 25% was eliminated in feces. In the plasma, no drug metabolite was detected that exceeded 10% of drug-related exposure. The main metabolites in urine were M3, M6, M16, and A1. The main products in feces were M1 and unchanged aprocitentan. Two metabolic pathways contributed to ≥25% of ¹⁴ C-radioactive elimination—glucosidation of aprocitentan to M3, and hydrolysis of aprocitentan to M1, which then undergoes other reactions leading to A1, A4, A5, M4, M5, M6, M11, M13, and M16.
Clearance	CL/F is approximately 0.3 L/h
Half-life	Terminal plasma half-life is approximately 46 hours, and effective half-life is approximately 41 hours
Metabolic pathway(s)	In the mass balance study, two metabolic pathways contributing to ≥25% of ¹⁴ C-radioactive elimination were detected: • Glucosidation of aprocitentan to M3 by UGT1A1 and UGT2B7 (accounts for approximately 25.2% of the administered dose) Hydrolysis of aprocitentan to M1 which then undergoes several other reactions leading to A1, A4, A5, M4, M5, M6, M11, and M13 (accounts for approximately 31.5% of the administered dose). M1 is formed by both chemical and enzymatic hydrolysis. It is believed that the hydrolysis is mostly chemical rather than enzymatic.
Primary excretion pathways (% dose)	After a single oral dose of radiolabeled aprocitentan, approximately 52% of the dose was eliminated via urine (0.2% unchanged) and 25% (6.8% unchanged) via feces.
	Intrinsic Factors and Specific Populations
Body weight	Based on popPK analysis, body weight does not affect PK to a clinically relevant extent (Section 14.5.2.5).
Age	Healthy elderly subjects (aged 65 to 80 years) C _{max} : 1.3-fold and AUC _T : 1.2-fold of that of healthy nonelderly subjects (aged 18 to 45 years)
Renal impairment	After a 50 mg dose of aprocitentan, compared to healthy subjects, the geometric mean ratio for C _{max} was 1.04 in those with severe renal impairment. The AUC _{0-t} and AUC _{0-∞} were 32% and 34% higher, respectively, in those with severe renal impairment compared to those with normal renal function.
Hepatic impairment	After a 25 mg dose of aprocitentan, compared to healthy subjects, the geometric mean ratios for C _{max} , AUC _{0-t} , and AUC _{0-∞} were 1.03, 1.2, and 1.2, respectively, in those with moderate hepatic impairment.

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro: induced CYP3A4; did not induce CYP1A2 or CYP2C9 In vitro: inhibited all members of the CYP2C family, CYP3A4, UGT1A1, and UGT2B7, with the strongest inhibition seen on CYP3A4; did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1 at therapeutic concentrations See Section 14.1 for more discussion on in vitro evaluation of drug interaction potential Clinical study: did not alter PK of midazolam or 1-hydroxy midazolam (CYP3A4 substrate) to a clinically relevant extent See Section 14.2 for more discussion on the clinical DDI study with midazolam
Inhibition/induction of transporter systems	In vitro: inhibited BCRP; did not inhibit P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K at therapeutic concentrations. Inhibition was also seen for NTCP (50µM) and BSEP (14µM) in vitro, compared to a C_{max} of about 6.8µM at a 25 mg dose. See Section 14.1 for more discussion in in vitro evaluation of drug interaction potential Clinical study: did not alter the PK of rosuvastatin (BCRP substrate) to a clinically relevant extent See Section 14.2 for more discussion on the clinical DDI study with rosuvastatin
	Immunogenicity (if Applicable)
Bioanalysis	Not applicable.
Incidence	Summarize incidence.
Clinical impact	Approximately one sentence each for impact on PK, impact on efficacy, impact on safety.

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Source: Summary of studies in Applicant's submission

Abbreviations: AUC_{0-∞}, area under the curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the curve from time 0 to time t; AUC_r, area under the concentration-time curve; BCRP, breast cancer resistance protein; BP, blood pressure; BSEP, bile salt export pump; CL/F, apparent clearance; CI, confidence interval; C_{max}, maximum plasma concentration; CV_{ln}, natural logarithmic coefficient of variation; CYP, cytochrome P450; EPC, established pharmacologic class; DDI, drug-drug interaction; ERA, endothelin receptor antagonist; ET, endothelin; h, hour; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MATE, multidrug and toxin extrusion transporter; NTCP, sodium-dependent taurocholate co-transporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P glycoprotein; PK, pharmacokinetic(s); popPK, population pharmacokinetics; T_{max}, time to peak concentration; UGT, uridine diphosphate- glucuronosyltransferase

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant has proposed a recommended (b) (4) dose of aprocitentan is 12.5 mg orally once daily, (b) (4). The Applicant's proposed dose (b) (4) based on the Applicant's interpretation of the results of the Phase 2 dose-finding study (Study AC-080A201) and Phase 3 study (PRECISION). The Phase 3 study evaluated doses of 12.5 mg and 25 mg vs. placebo in a parallel arm design. These doses were selected based on

the results of the Phase 2 dose-finding study and Phase 1 pharmacodynamic study (Study AC-080-102), which suggested that doses of aprocitentan in the range of 10 mg to 25 mg might provide the best benefit/risk profile. The phase 3 study also evaluated the 25 mg dose in a randomized withdrawal period.

Data Supporting Dose Selection for the Applicant's Phase 3 Study

In the Phase 2 dose-finding study, subjects with essential hypertension were randomized to receive aprocitentan (5, 10, 25, or 50 mg), 20 mg lisinopril, or placebo for 8 weeks. Aprocitentan doses of 10, 25, and 50 mg decreased sitting systolic/diastolic unattended automated office blood pressure measurement (uAOBPM) from baseline to Week 8, with placebo-corrected reductions of 7.1/4.9, 9.9/7.0, and 7.6/5.0 mmHg, respectively, compared with a reduction of 4.8/3.8 mmHg with lisinopril 20 mg. For those with valid ambulatory blood pressure monitor readings, aprocitentan 10, 25, and 50 mg significantly decreased placebo-corrected 24-hour systolic/diastolic blood pressure by 4.0/4.0, 4.8/5.9, and 3.7/4.5 mmHg, respectively. Based on the Phase 2 study results, the Applicant noted that the maximum effect on blood pressure appeared to correspond to the 25 mg dose, with similar effects on both uAOBPM and ambulatory blood pressure monitoring (ABPM) readings at the 10 mg and 50 mg doses. For additional discussion of the Phase 2 study results, see Section [14.2](#).

The Applicant also conducted a Phase 1 study to better understand the relationship between the dose of aprocitentan and risk of fluid retention (as assessed by changes in body weight). In this Phase 1 study, healthy male subjects on a high sodium diet were randomized to placebo or aprocitentan doses of 10, 25, or 50 mg, and to one of two treatment sequences (A-B or B-A). Treatment A received aprocitentan once daily from Day 1 to Day 9, and Treatment B received placebo from Day 1 to Day 9. The 10 mg dose was considered to be “non-inferior” to placebo because the upper limit of the 90% confidence interval (CI) of body weight increase did not exceed 1 kg (mean increase of +0.4 kg, CI 0.05-0.8). In contrast, the 25 mg and 50 mg doses had an upper limit of the 90% CI that exceeded 1 kg (mean body weight increases of +0.8 kg, CI 0.03-1.5 and +0.8 kg, CI 0.3-1.3, respectively), suggesting a greater risk at the 25 mg as compared to the 10 mg dose. For additional discussion of the results of Study AC-080-102, see Section [14.2](#).

Findings in Applicant's Phase 3 Study

As discussed in Section [6.2](#), the Applicant's Phase 3 study was a multipart study in adults with a systolic blood pressure (SBP) ≥ 140 mmHg (based on uAOBPM) who were prescribed at least three antihypertensive medications. In Part 1 of the study, 730 subjects were randomized 1:1:1 to aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo once daily for a 4-week double-blind treatment period. The mean ($\pm$ SE) change in SBP at 4 weeks was -15.3 ± 0.9 mmHg for aprocitentan 12.5 mg, -15.2 ± 0.9 mmHg for 25 mg, and -11.5 ± 0.9 mmHg for placebo, for a difference versus placebo of -3.8 ± 1.3 mmHg (97.5% CI: -6.8, -0.8; $p = 0.004$) and -3.7 ± 1.3 mmHg (97.5% CI: -6.7, -0.8; $p = 0.005$), respectively. The results of exploratory analyses based on other blood pressure parameters (e.g., mean sitting diastolic blood pressure [SiDBP]) measured by automated office blood pressure measurement (AOBPM), 24 hour mean SBP measured by ABPM, 24 hour mean diastolic blood pressure (DBP) measured by ABPM, daytime mean SBP measured by ABPM, daytime mean DBP measured by ABPM, night-time mean SBP

measured by ABPM, and night-time mean DBP measured by ABPM) are shown in [Table 6](#). Based on the Applicant’s point estimates, the difference in BP response, if real, is modest.

Table 6. Differences Between Aprocitentan 25 mg and 12.5 mg for Blood Pressure Endpoints

Endpoint	LS Mean change 25 mg	LS Mean change 12.5 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in mean trough SiSBP (primary endpoint)	-15.20	-15.26	0.06	-0.4
Change from baseline to Week 4 in mean trough SiDBP	-10.95	-10.43	-0.53	5.1
Change from baseline to Week 4 in 24 h mean SBP	-8.44	-6.73	-1.71	25.5
Change from baseline to Week 4 in 24 h mean DBP	-7.74	-6.25	-1.49	23.9
Change from baseline to Week 4 in daytime mean SBP	-7.72	-6.22	-1.50	24.1
Change from baseline to Week 4 in daytime mean DBP	-8.10	-6.11	-1.99	32.6
Change from baseline to Week 4 in night-time mean SBP	-10.47	-8.14	-2.33	28.6
Change from baseline to Week 4 in night-time mean DBP	-8.21	-6.91	-1.30	18.8

Source: Applicant-generated table from response to May 4, 2023 Information Request, document number D-23.205, Table 1

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

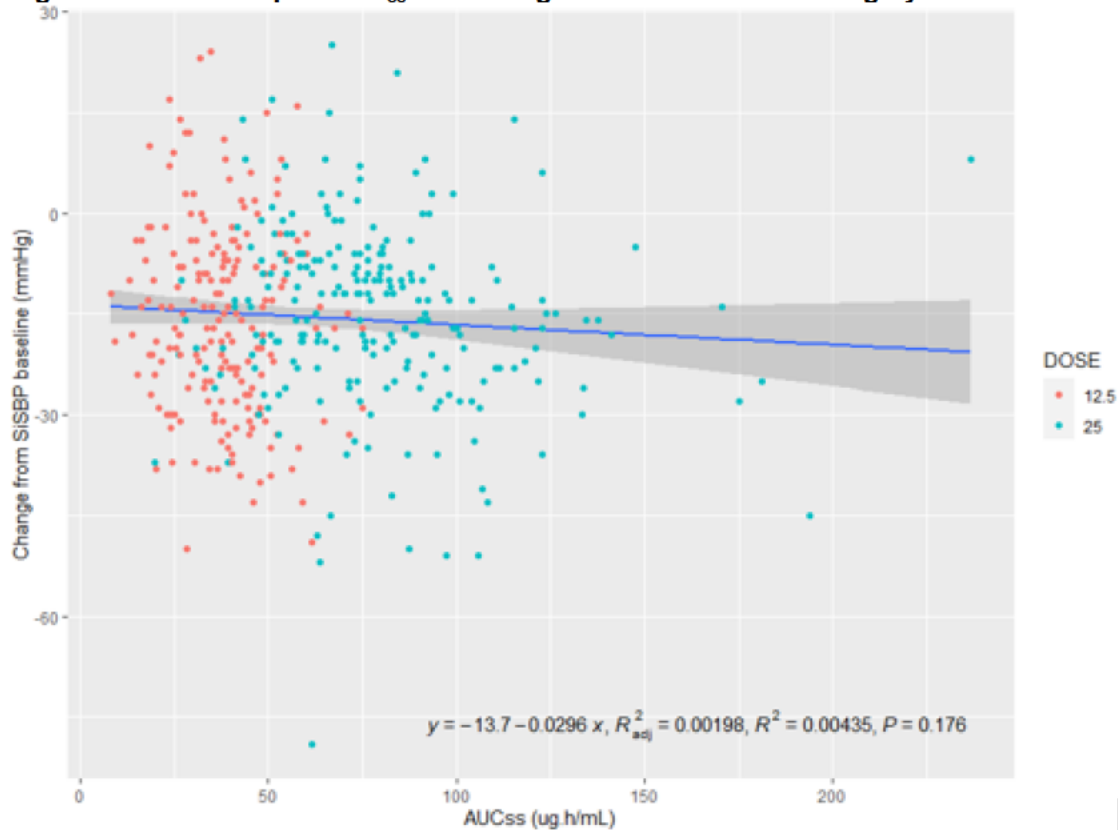
** Of the LS mean in the 12.5 group (positive values indicate a benefit for 25 mg)

N is different for each endpoint.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; h, hours; LS, least squares; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

According to the pharmacometric reviewer’s assessment, there does not appear to be a difference in efficacy between the 12.5 and 25 mg dose for change from baseline in sitting systolic blood pressure (SiSBP), as demonstrated by a very shallow exposure-response relationship ([Figure 1](#)).

Figure 1. Relationship of AUC_{ss} and Change From Baseline in Sitting Systolic Blood Pressure



Source: Reviewer-independent assessment

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state, SiSBP, sitting systolic blood pressure

In sum, while the aforementioned findings appear to support the (b) (4) dose (12.5 mg) proposed by the Applicant, (b) (4)

(b) (4). ABPM data suggest that there may be some improvement between the 12.5 mg and 25 mg dose; however, the improvement is minimal and of uncertain clinical relevance. For further discussion of this issue, see Section 6.3.

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. PRECISION Study

6.2.1.1. PRECISION Study Design

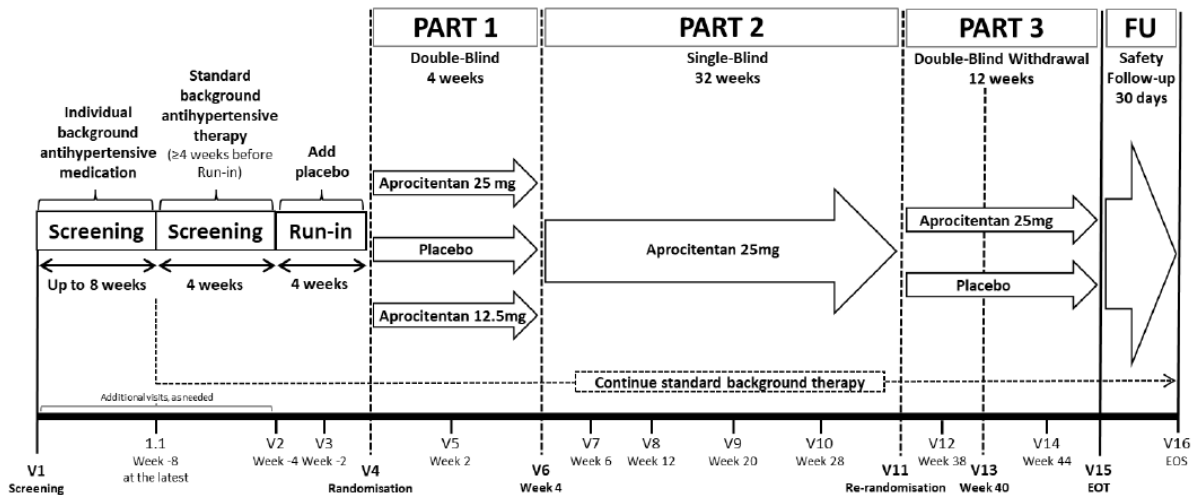
Study Design

The efficacy of aprocitentan was evaluated in a multipart, Phase 3 multicenter study (PRECISION) in adults with SBP ≥ 140 mmHg who were prescribed at least three antihypertensive medications. The study included a placebo run-in period which was followed by three parts, as described below. Prior to the placebo run-in period, all subjects were switched to

standard background antihypertensive therapy (SBAT) consisting of an ARB (valsartan, 160 mg), a calcium channel blocker (amlodipine, 5 or 10 mg), and a diuretic (hydrochlorothiazide, 25 mg). SBAT was continued throughout the study. Subjects with concomitant use of a stable dose of a beta blocker (any indication) that was initiated at least 4 weeks prior to the screening visit continued this treatment throughout the study.

Following the 4-week placebo run-in period, 730 subjects (whose SiSBP (uAOBPM) remained ≥ 140 mmHg) were randomized 1:1:1 to aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo once daily for the initial 4-week double-blind (DB) treatment period (Part 1). At the end of 4 weeks, all subjects entered the single-blind treatment period (Part 2) where they received aprocitentan 25 mg once daily for 32 weeks. At the end of the 32 weeks, subjects were rerandomized to receive either aprocitentan 25 mg or placebo, once daily, during a 12-week DB-withdrawal (WD) period (Part 3) (Figure 2). All subjects then entered a 30-day safety follow-up period.

Figure 2. PRECISION Study Design



Source: PRECISION clinical study report
Abbreviations: EOS, end of study; EOT, end of treatment; FU, follow-up; V, visit

Objectives

The primary objective was to demonstrate the BP-lowering effect of aprocitentan when added to standard-of-care in subjects with true resistant hypertension³ (RHT).

The secondary objectives were: (1) to demonstrate that the effect of aprocitentan on BP is durable when added to standard-of-care in subjects with true RHT, and (2) to evaluate the long-term safety and tolerability of aprocitentan in subjects with true RHT during 48 weeks of treatment.

³ Resistant hypertension was defined as subjects who failed to achieve their recommended BP treatment target with maximum tolerated doses of an appropriate regimen of 3 antihypertensive drugs from different classes. Subjects with pseudoresistant hypertension were to be excluded from the study (e.g., inappropriate blood pressure measurement, white coat effect, insufficient efforts to optimize therapy, or poor adherence).

Endpoints

The primary efficacy endpoint was the change from baseline to Week 4 of double-blind treatment in mean trough SiSBP, recorded via uAOBPM. Baseline was defined as the last available measurement before the start of DB treatment.

The key secondary efficacy endpoint was the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP, recorded via uAOBPM.

Unattended Automated Office Blood Pressure Measurements

The blood pressure procedures used for assessments followed the American Heart Association guidelines/Canadian Education Program on Hypertension ([Pickering et al. 2005](#); [Daskalopoulou et al. 2012](#)). Unattended automated office blood pressure was measured throughout the study with an automatic oscillometric sphygmomanometer which was provided to each site by the central blood pressure laboratory. At each study visit, blood pressure was measured noninvasively from the same arm by the provided AOBPM device, which recorded multiple sitting blood pressure readings with the subject resting undisturbed and unattended in a quiet place for five minutes. At each assessment, SiSBP and SiDBP were measured five times with a 1-minute time interval between them. After discarding the first reading, the blood pressure device/system generated the average of the remaining four readings for SiSBP and SiDBP. Blood pressure was measured at trough (i.e., before taking the study treatment and the standardized background antihypertensive therapy) at around the same clock time.

The baseline uAOBPM was defined as the last available measurement before or on the day of randomization. The DB-WD baseline (Week 36) was defined as the last available measurement before or on the day of rerandomization.

For additional details, including procedures for assessing other blood pressure parameters, see Section [15](#).

6.2.1.2. Eligibility Criteria, PRECISION Study

6.2.1.2.1. Key Inclusion Criteria

Screening Criteria

- Male or female patients 18 years (or year of country-specific majority) or older.
- Historical documentation in the subject's medical records of uncontrolled BP, despite at least three background antihypertensive medications within 1 year before the screening visit.
- Treatment with at least three antihypertensive therapies of different pharmacological classes for at least 4 weeks before the screening visit.⁴
- Mean SiSBP $\geq$ 140 mmHg recorded via uAOBPM at the screening visit.

⁴ Requirement to include a diuretic as 1 of the 3 antihypertensives was removed in Global Protocol Amendment 2 (protocol version 3.0) dated February 27, 2020.

- Documentation in the subject's medical records of diagnosis of RHT according to the site's medical practice:
 - Exclusion of secondary causes of hypertension (through serum aldosterone, plasma renin activity, duplex/doppler ultrasonography, computer tomography angiography assessments).
 - Adherence to medication (e.g., how the adherence was checked and/or monitored) to eliminate apparent RHT.
- Women of childbearing potential⁵ were eligible only if the following applied:
 - Negative pregnancy test at screening and at baseline (i.e., end of placebo run-in [RI] period).
 - Agreement to undertake pregnancy tests during the study and up to 30 days after randomized study treatment discontinuation.
 - Agreement to use accepted methods of birth control⁶ from screening up to at least 30 days after randomized study treatment discontinuation.
- Mean trough SiSBP ≥ 140 mmHg (uAOBPM) at the switch from individual background antihypertensive medications (i.e., at least three medications from different pharmacological classes) to SBAT.

RI Entry Criteria

- Switched to SBAT at least 4 weeks before the first run-in visit.
- Mean trough SiSBP ≥ 140 mmHg (uAOBPM) despite administration of SBAT for at least 4 weeks.

Randomization Entry Criteria (End of RI)

- Stable dose of SBAT for at least 1 week before Day -1 (end of the placebo RI period).
- Mean trough SiSBP ≥ 140 mmHg (uAOBPM) despite administration of placebo for 4 weeks on top of SBAT.
- Subjects demonstrating $\geq 80\%$ adherence (by pill counting) to study treatment (i.e., placebo) and to SBAT during the placebo RI period.

⁵ A woman was considered of childbearing potential unless she met at least one of the following criteria: (1) Previous bilateral salpingectomy, bilateral salpingo-oophorectomy, or hysterectomy; (2) Postmenopausal, i.e., 12 consecutive months with no menses without an alternative medical cause [ICH 2009]; (3) Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

⁶ Acceptable methods of contraception included the use of one method from one of the following options: (1) standard intrauterine device, intrauterine system, progesterone implant, or tubal sterilization; (2) estrogen and progesterone oral contraceptives, estrogen and progesterone transdermal patch, vaginal ring, or progesterone injection; (3) diaphragm with spermicide or cervical cap with spermicide PLUS male condom; (4) partner vasectomy plus male condom, diaphragm with spermicide, cervical cap with spermicide, estrogen and progesterone oral contraceptive, estrogen and progesterone transdermal patch, vaginal ring, or progesterone injection.

6.2.1.2.2. Key Exclusion Criteria

Screening Period Criteria

Disease/Condition

- Pregnant or lactating subjects.
- Apparent/pseudo RHT due to white coat effect, medical inertia, poor therapeutic adherence, or secondary causes of hypertension (not including obstructive sleep apnea).
- Confirmed severe hypertension (grade 3): mean SiSBP ≥ 180 mmHg and/or SiDBP ≥ 110 mmHg, recorded via uAOBPM at two different time points. The BP remeasurement could be during the screening visit (e.g., after at least 3 hours), or at the next planned visit, or at an unscheduled visit. The time of remeasurement was at the Investigator's discretion, taking into consideration the subject's medical history.
- Documented transient ischemic attack, stroke, unstable angina, or myocardial infarction within 6 months prior to screening.
- Clinically significant unstable cardiac disease at screening or in the past, in the opinion of the Investigator, e.g., uncontrolled symptomatic arrhythmia, atrial fibrillation, congestive heart failure NYHA stage II with relevant mitral valve insufficiency and/or aortic stenosis, congestive heart failure NYHA stage III or IV.
- Severe renal insufficiency defined as an eGFR per the chronic kidney disease-epidemiology collaboration creatinine equation < 15 mL/min/1.73 m².
- Type 1 diabetes mellitus
- Subjects working night shifts⁷
- Known concomitant life-threatening disease with a life expectancy < 18 months after screening.

Treatments

- Treatment with any medication which may affect BP and/or treatment with a high dose of loop diuretics (i.e., furosemide > 80 mg/day, or equivalent dosage of other loop diuretics).
- Treatment with any other ERAs.
- Contraindication and/or known hypersensitivity to any of the three components of the SBAT (fixed combination of CCB [amlodipine], ARB [valsartan] and diuretic [hydrochlorothiazide]), according to their labels, or drugs of the same class, or to any of the excipients.
- Known hypersensitivity to aprocitentan or drugs of the same class, or any of the excipients.
- Treatment with another investigational treatment within 3 months prior to screening.

⁷ A maximum of 2 night shifts per week was permitted except within 3 days prior to a study visit. Night shifts were not allowed during visits at which ABPM was recorded.

Laboratory Assessments

- Confirmed laboratory assessments based on central laboratory:
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>3 \times$ upper limit of normal (ULN), or severe hepatic impairment
 - Hemoglobin <10 g/L
 - NT-proBNP ≥ 500 pg/mL

Placebo Run-In Period Exclusion Criteria

- Confirmed severe hypertension (grade 3) defined as mean SiSBP ≥ 180 mmHg and/or SiDBP ≥ 110 mmHg recorded via uAOBPM at two different time points. The BP remeasurement could be during the first run-in visit (e.g., after at least 3 hours), or at the next planned visit, or at an unscheduled visit. The time of remeasurement was at the Investigator's discretion, taking into consideration the subject's medical history.

Randomization Exclusion Criteria

- Laboratory assessments based on local laboratory:
 - ALT or AST $>3 \times$ ULN
 - Hemoglobin <10 g/L
 - eGFR per the chronic kidney disease-epidemiology creatinine equation <15 mL/min/1.73 m²

6.2.1.3. Statistical Analysis Plan, PRECISION Study

Analysis Sets

Full Analysis Set (FAS): All subjects who were randomized and have a baseline SiSBP recorded via uAOBPM.

Modified FAS: All subjects from the FAS who were rerandomized in the DB-WD part of the study and who have a DB-WD baseline SiSBP recorded via uAOBPM.

Sample Size Calculation

The Applicant planned the sample size based on the secondary endpoint to maintain at least 85% power for the DB-WD period (Part 3). At least 600 subjects were to be randomized and at least 380 subjects were expected to be re-randomized in the DB-WD period.

Specifically, a sample size of 380 would provide 90% power to detect difference of 5 mmHg between aprocitentan 25 mg and placebo at two-sided alpha of 0.05, assuming the within-group SD for the change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP as measured by uAOBPM was around 15 mmHg (based on Study AC-080A201).

Primary Analysis

The primary analysis was conducted on the FAS for the three treatment groups (aprocitentan 25 mg, aprocitentan 12.5 mg, and placebo). The primary endpoint, change from baseline to Week 4 (Part 1) in mean trough SiSBP measured by uAOBPM, was analyzed using a mixed-effects model for repeated measures (MMRM) analysis with factors for treatment group, visit and treatment by visit interaction, and covariates for baseline SiSBP and the interaction between baseline SiSBP and visit. An unstructured covariance matrix was used to account for the within subject correlation.

Intercurrent Event/Missing Data Handling

A treatment policy strategy was used to handle intercurrent events including “Premature discontinuation of DB treatment,” “the addition / dose increase of a diuretic,” and “use of rescue medication” in the primary and secondary analyses (i.e., all uAOBPM measurements, irrespective of any intercurrent event(s), were to be included in the analysis).

Missing data were not to be imputed but were to be handled by a mixed model based on the assumption that the data were missing at random (MAR).

Sensitivity Analyses

The impact of deviations from the MAR assumption was to be assessed by the following sensitivity analyses:

- Copy reference multiple imputation
- Jump to reference multiple imputation
- Tipping point analysis

Alternative estimand for treatment discontinuation and rescue medication:

- Hypothetical strategy (i.e., uAOBPM recordings obtained more than 1 day after premature discontinuation of double-blind treatment were excluded from the main analysis (i.e., considered missing). uAOBPM recordings obtained after the addition of a diuretic, or use of rescue medication, were also excluded from the analysis.)

Additional sensitivity analysis:

- The primary analysis was to be performed excluding site 4204 given data integrity concerns at the site (as per internal audit report).

Subgroup Analyses

The following subgroups were prespecified:

- Age at screening (years): 18 to <65, 65 to <75, and ≥ 75
- Sex: male, female
- Weight at baseline (kg): ≤ 100 , > 100

- Body mass index (BMI) at screening (kg/m²): <30, 30 to <40, ≥40
- Race: Black or African American, White, Asian, Other
 - ‘Other’ includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other. The ‘Other’ category was not considered for subgroup analyses due to the mix of races and small number of subjects limiting the ability (i.e., low power) to detect differences between treatment groups.
- Region: Asia/Australia, Europe, North America
- Urine albumin-to-creatinine ratio (UACR) at baseline (mg/g): <30, 30 to 300, >300
- Chronic kidney disease (CKD) stage at baseline (eGFR, mL/min/1.73 m²): Stage 1 or 2 (eGFR ≥60), Stage 3 or 4 (eGFR 15 to <60)
- Diabetes (medical history): Yes/No

Protocol Version 1/2 versus protocol Version 3 at randomization: compared to the prior versions of the protocol, in protocol Version 3 Amendment 2, diuretics were no longer required to be one of the three antihypertensive classes for enrollment in the study.

Subgroups were to be analyzed using the same model as the primary analysis. Interaction p-values were obtained from adding subgroup by treatment and subgroup by treatment by visit interaction terms to the primary analysis model.

Secondary Analysis

The secondary analysis (at randomized withdrawal phase) was to be conducted on the modified FAS for the two treatment groups (aprocitentan 25 mg and placebo). The secondary endpoint, change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP recorded via uAOBPM, was analyzed using a mixed model with factors for stratum (i.e., randomized treatment in Part 1), treatment group, visit, and treatment by visit interaction, and covariates for DB-WD baseline SiSBP and the interaction between DB-WD baseline SiSBP and visit, and an unstructured covariance matrix.

Similar sensitivity analyses as for the primary analysis were to be conducted.

Testing Strategy

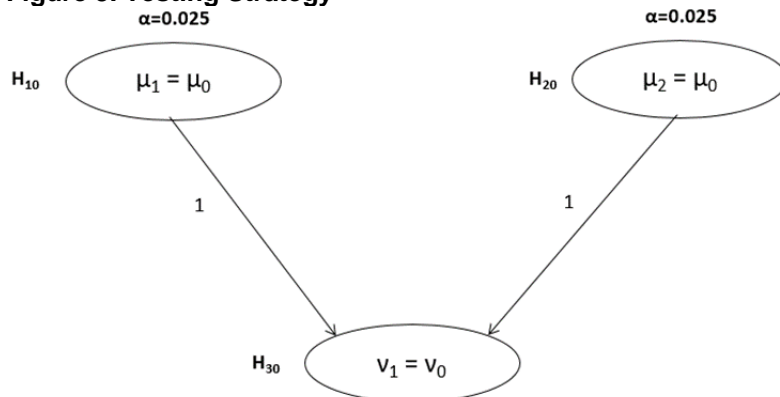
Three null hypotheses were to be tested in the study. The first two were based on the primary endpoint in DB Part 1, the third hypothesis was based on the secondary endpoint at DB-WD Part 3 ([Figure 3](#)).

- *First null hypothesis (H10)*: there was no difference between aprocitentan 25 mg and placebo in the mean change from baseline to Week 4 in mean trough SiSBP in Part 1.
- *Second null hypothesis (H20)*: there was no difference between aprocitentan 12.5 mg and placebo in the mean change from baseline to Week 4 in mean trough SiSBP in Part 1.

- *Third null hypothesis (H30):* there was no difference between aprocitentan 25 mg and placebo in the mean change from DB-WD baseline (Week 36) to Week 40 in mean trough SiSBP in Part 3.

The first two (H10 and H20) were tested in parallel using the Bonferroni correction (each with a two-sided alpha of 0.025), and the third (H30) was only to be tested if H10 or H20 was rejected.

Figure 3. Testing Strategy



Source: Applicant's statistical analysis plan

Abbreviations: α , level of significance; H₁₀, first null hypothesis; H₂₀, second null hypothesis; H₃₀, third null hypothesis; μ , population mean; V, mean changes from baseline for each endpoint

Statistical Analysis Plan Versions

The study was conducted from June 18, 2018 (first subject, first visit) to April 25, 2022 (last subject, last visit). Version 1 of the statistical analysis plan (SAP) was finalized on April 4, 2019. The SAP was subsequently amended twice. Version 2 was finalized on September 23, 2021. In this amendment, the details of the reference based multiple imputation were added. Version 3 of the SAP (the latest version) was finalized on April 6, 2022. In this amendment, the primary estimand was changed from using a hypothetical strategy to a treatment policy strategy based on the Agency's feedback.

The changes that were made to the SAP via these amendments do not raise concerns about the interpretability of the study results.

6.2.1.4. Results of Analyses, PRECISION Study

The section that follows provides an overview of patient disposition in the overall trial, followed by a discussion of Part 1 and Part 3.

Overall Disposition

In the PRECISION study, 1965 subjects were screened, and 730 subjects were randomized to aprocitentan 25 mg (N=243), aprocitentan 12.5 mg (N=243) and placebo (N=244). [Table 7](#) shows the disposition of subjects (based on their assigned treatment group in Part 1). Overall, of the 730 randomized subjects, 153 (20.1%) discontinued study treatment and 68 (9.3%) discontinued the study at some point during any of the three parts of the study ([Table 7](#)). Over the course of the three parts of the study, the main reasons for study treatment discontinuation

were “adverse event”, “withdrawal by subject” and “other.” The main reasons for study discontinuation were “withdrawal by subject”, “death” and “other.”

Table 7. Overall Disposition, PRECISION Study

Parameter	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=243 n (%)	Placebo N=244 n (%)	Total N=730 n (%)
Screened				1965
Randomized (FAS)	243 (100)	243 (100)	244 (100)	730 (100)
Rerandomized (mFAS)	201 (82.7)	208 (85.6)	205 (84.0)	614 (84.1)
Prematurely discontinued study treatment (during any study part)	55 (22.6)	46 (18.9)	52 (21.3)	153 (20.1)
Adverse event	18(7.4)	13(5.3)	22(9.0)	53(7.3)
Withdrawal by subject	9(3.7)	11(4.5)	9(3.7)	29(4.0)
Lost to follow-up	4(1.6)	2(0.8)	3(1.2)	9(1.2)
Death	5(2.1)	0 (0.0)	0 (0.0)	5(0.7)
Lack of efficacy	0 (0.0)	1(0.4)	0 (0.0)	1(0.1)
Pregnancy	0 (0.0)	1(0.4)	0 (0.0)	1(0.1)
Other	19(7.8)	18(7.4)	18(7.4)	55(7.5)
Prematurely discontinued study (during any study part)	26 (10.7)	22 (9.1)	20 (8.2)	68 (9.3)
Withdrawal by subject	10(4.1)	7(2.9)	7(2.9)	24(3.3)
Death	7(2.9)	4(1.6)	1(0.4)	12(1.6)
Lost to follow-up	4(1.6)	2(0.8)	3(1.2)	9(1.2)
Adverse event	1(0.4)	2(0.8)	4(1.6)	7(1.0)
Other	4(1.6)	7(2.9)	5(2.0)	16(2.2)

Source: Statistical reviewer's analysis; adsl.xpt

Abbreviations: FAS, full analysis set; mFAS, modified full analysis set; n, number of subjects in subset; N, overall number of subjects

Results of Part 1

Demographic

Baseline demographics in Part 1 were balanced among the treatment arms ([Table 8](#)). The median age was 63 years (range 24 to 84 years). At baseline, 44% of subjects were aged ≥ 65 years. Approximately 60% of subjects were male. The majority of subjects were white (83%); 11% were Black or African American, and 5% were Asian. Approximately 10% were Hispanic or Latino ([Centers for Disease Control and Prevention 2023](#)).⁸ The study was an international study and of those enrolled, approximately 32% were enrolled at sites in North America. Of those enrolled at U.S. sites, 37% were Black or African American.

⁸ Per the National Health and Nutrition Examination Survey (NHANES) conducted between 2017-2018, in the United States, approximately 51% of men, 75% of those ≥ 60 years old, 57% of non-Hispanic Black adults, 44% of non-Hispanic white adults, and 44% of Hispanic adults met the definition of hypertension as defined by the 2017 ACC/AHA guideline (i.e., BP $>130/80$ mmHg).

Table 8. Baseline Demographics, Part 1, FAS

Parameter	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=243	Placebo N=244	Total N=730
Age (years)				
Mean (SD)	61.2 (10.31)	61.7 (10.36)	62.2 (11.15)	61.7 (10.61)
Median	61.0	63.0	64.0	63.0
IQR	54.0, 69.0	55.0, 69.0	56.0, 70.0	55.0, 69.0
Min, max	30.0, 84.0	24.0, 83.0	29.0, 83.0	24.0, 84.0
Age, years, n (%)				
18 to <65	143 (58.8)	136 (56.0)	130 (53.3)	409 (56.0)
65 to <75	78 (32.1)	85 (35.0)	86 (35.2)	249 (34.1)
≥75	22 (9.1)	22 (9.1)	28 (11.5)	72 (9.9)
Sex, n (%)				
Female	99 (40.7)	98 (40.3)	99 (40.6)	296 (40.5)
Male	144 (59.3)	145 (59.7)	145 (59.4)	434 (59.5)
Race, n (%)				
Asian	11 (4.5)	14 (5.8)	13 (5.3)	38 (5.2)
Black or African American	28 (11.5)	28 (11.5)	26 (10.7)	82 (11.2)
Native Hawaiian or other Pacific Islander	1 (<1)	0	0	1 (<1)
Other	0	0	1 (<1)	1 (<1)
White	203 (83.5)	200 (82.3)	202 (82.8)	605 (82.9)
Missing	0	1 (<1)	2 (<1)	3 (<1)
Ethnicity, n (%)				
Hispanic or Latino	28 (11.5)	22 (9.1)	23 (9.4)	73 (10.0)
Not Hispanic or Latino	213 (87.7)	219 (90.1)	218 (89.3)	650 (89.0)
Missing	2 (<1)	2 (<1)	3 (1.2)	7 (1.0)
Region, n (%)				
Asia/Australia	14 (5.8)	19 (7.8)	17 (7.0)	50 (6.8)
Europe	153 (63.0)	143 (58.8)	152 (62.3)	448 (61.4)
North America	76 (31.3)	81 (33.3)	75 (30.7)	232 (31.8)

Source: Statistical reviewer's analysis; adsl.xpt

Abbreviations: FAS, full analysis set; IQR, interquartile range; max, maximum; min, minimum; n, number of subjects in subset; N, overall number of subjects; SD, standard deviation

Baseline Clinical Characteristics

Disease characteristics at baseline/screening were balanced across treatment groups. At screening, the mean (SD) SiSBP and SiDBP were 156.9 (11.6) mmHg and 88.5 (10.6) mmHg, respectively. At screening, approximately 63% of subjects reported taking ≥4 antihypertensives. (Table 9). At baseline, approximately 19% had an eGFR <60 mL/min/1.73 m², 69% had a BMI ≥30 kg/m², 54% had type 2 diabetes, 31% had ischemic heart disease, and 20% had congestive heart failure.

Table 9. Baseline Disease Characteristics, Part 1, FAS

Parameter	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=243	Placebo N=244	Total N=730
BMI (kg/m ²) at screening				
Mean (SD)	33.6 (6.2)	34.3 (6.8)	33.3 (5.6)	33.7 (6.2)
Median	32.6	33.4	32.7	32.9
IQR	29.4, 37.0	29.2, 38.0	29.0, 37.1	29.3, 37.5
Min, max	18.0, 57.6	22.3, 63.9	19.4, 50.6	18.0, 63.9

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Parameter	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=243	Placebo N=244	Total N=730
BMI (kg/m ²) groups, n (%)				
<25	10 (4.1)	11 (4.5)	15 (6.1)	36 (4.9)
25 to <30	65 (26.7)	59 (24.3)	64 (26.2)	188 (25.8)
30 to <40	135 (55.6)	132 (54.3)	132 (54.1)	399 (54.7)
≥40	33 (13.6)	41 (16.9)	33 (13.5)	107 (14.7)
Time from first diagnosis of hypertension to screening (years)				
Mean (SD)	16.6 (10.83)	15.7 (9.79)	17.0 (10.38)	16.5 (10.34)
Median	14.3	15.3	16.4	15.3
IQR	9.1, 21.7	8.8, 21.3	8.9, 22.1	8.9, 21.7
Min, max	0.1, 64.9	0.7, 48.7	0.0, 49.8	0.0, 64.9
Missing	1	0	0	1
Number of antihypertensive therapies at screening, n (%)				
<3	0	0	1	1 (0.1)
3	92 (37.9)	85 (35.0)	92 (37.7)	269 (36.8)
4	116 (47.7)	111 (45.7)	110 (45.1)	337 (46.2)
≥5	35 (14.4)	47 (19.3)	41 (16.8)	123 (16.8)
Use of specific antihypertensive therapies at screening, n(%)				
Renin-angiotensin system blockers	239 (98.4)	237 (97.5)	240 (98.4)	716 (98.1)
Calcium channel blockers (CCB)	205 (84.4)	199 (81.9)	209 (85.7)	613 (84.0)
Diuretics	214 (88.1)	208 (85.6)	213 (87.3)	635 (87.0)
Beta-blockers	151 (62.1)	160 (65.8)	145 (59.4)	456 (62.5)
SiSBP (mmHg) at screening				
Mean (SD)	156.7 (11.58)	157.2 (11.90)	156.8 (11.36)	156.9 (11.60)
Median	156.0	155.0	155.0	155.0
IQR	148.0, 166.0	147.0, 166.0	148.5, 164.0	148.0, 165.0
Min, max	120.0, 207.0	133.0, 210.0	126.0, 202.0	120.0, 210.0
Missing	1	4	0	5
SiDBP (mmHg) at screening				
Mean (SD)	88.7 (10.75)	89.0 (10.32)	87.7 (10.62)	88.5 (10.57)
Median	89.0	89.0	87.0	89.0
IQR	81.0, 96.0	81.0, 96.0	81.0, 95.0	81.0, 96.0
Min, max	60.0, 130.0	60.0, 131.0	63.0, 127.0	60.0, 131.0
Missing	1	4	0	5
UACR (mg/g) category, n (%)				
30-300	63 (25.9)	55 (22.6)	56 (23.0)	174 (23.8)
<30	144 (59.3)	155 (63.8)	154 (63.1)	453 (62.1)
>300	34 (14.0)	28 (11.5)	28 (11.5)	90 (12.3)
Missing	2 (<1)	5 (2.1)	6 (2.5)	13 (1.8)
eGFR (ml/min/1.73 m ²) category, n (%)				
<30	8 (3.3)	7 (2.9)	6 (2.5)	21 (2.9)
30 to <45	17 (7.0)	21 (8.6)	10 (4.1)	48 (6.6)
45 to <60	30 (12.3)	33 (13.6)	30 (12.3)	93 (12.7)
≥60	188 (77.4)	182 (74.9)	198 (81.1)	568 (77.8)

Parameter	Aprocitentan	Aprocitentan	Placebo N=244	Total N=730
	12.5 mg N=243	25 mg N=243		
Medical history, n (%)				
Diabetes	131 (53.9)	136 (56.0)	128 (52.5)	395 (54.1)
Ischemic heart disease	73 (30.0)	79 (32.5)	73 (29.9)	225 (30.8)
Congestive heart failure	48 (19.8)	50 (20.6)	45 (18.4)	143 (19.6)

Source: Statistical reviewer's analysis; adbasco.xpt. Data on medical history, number of antihypertensives, and use of specific antihypertensive therapies at screening are based on the Applicant's analyses

Abbreviations: BMI, body-mass index; eGFR, estimated glomerular filtration rate; FAS, full analysis set; IQR, interquartile range; max, maximum; min, minimum; n, number of subjects in subset; N, overall number of subjects; SD, standard deviation; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure; UACR, urine albumin-to-creatinine ratio

Disposition

Among the 730 randomized subjects, 26 (3.6%) discontinued treatment and 8 (1.1%) discontinued the study during Part 1 ([Table 10](#)); a total of 704 (96.4%) subjects in Part 1 entered Part 2. Numbers of treatment discontinuation and study discontinuation were small. The most common reason for study drug discontinuation in the aprocitentan groups was adverse event. There was 1 death during Part 1 in the aprocitentan 12.5 mg group. For further information, see [Section 7.6.2](#).

Table 10. Disposition, Part 1, FAS

Parameter	Aprocitentan	Aprocitentan	Placebo N=244 n (%)	Total N=730 n (%)
	12.5 mg N=243 n (%)	25 mg N=243 n (%)		
Randomized	243 (100)	243 (100)	244 (100)	730 (100)
Discontinued study drug (during Part 1)	11 (4.5)	9 (3.7)	6 (2.5)	26 (3.6)
Adverse event	6(2.5)	5(2.1)	2(0.8)	13(1.8)
Other	3(1.2)	2(0.8)	3(1.2)	8(1.1)
Withdrawal by subject	2(0.8)	2(0.8)	1(0.4)	5(0.7)
Discontinued study (during Part 1)	5 (2.1)	1 (0.4)	2 (0.8)	8 (1.1)
Withdrawal by subject	1 (0.4)	1 (0.4)	0 (0)	2 (0.3)
Death	1 (0.4)	0 (0)	0 (0)	1 (0.1)
Adverse event	1 (0.4)	0 (0)	1 (0.4)	2 (0.3)
Other	2 (0.8)	0 (0)	1 (0.4)	3 (0.4)

Source: Statistical reviewer's analysis; adsl.xpt

Abbreviations: FAS, full analysis set; n, number of subjects in subset; N, overall number of subjects; SD, standard deviation

Analyses of Primary Endpoint

The primary endpoint of change from baseline in SiSBP at Week 4 was analyzed using an MMRM model. Because of concerns with the Applicant's prespecified analytic approach (i.e., that the approach to handling missing data was not reasonable and was in violation of the intent-to-treat [ITT] principle), the review team used a different method to analyze the primary endpoint (see "*Missing data handling and FDA recommended primary analysis*" below for further discussion of this issue). Based on the primary analysis recommended by FDA, statistical significance was demonstrated at a two-sided alpha level of 0.025 for aprocitentan 12.5 mg versus placebo [least square mean (LSM) difference: -3.8 mmHg; 97.5% CI:-6.8, -0.8; p-value=0.0043], and for aprocitentan 25 mg versus placebo [LSM difference: -3.7 mmHg; 97.5% CI:-6.6, -0.7; p-value=0.0054] ([Table 11](#)). The results are similar to the Applicant's prespecified

analysis. See Section 6.3.1 for a discussion of the clinical meaningfulness of the treatment effect for the two doses of aprocitentan evaluated.

There was no planned statistical comparison of the two aprocitentan doses, but point estimates and confidence intervals for treatment effects were numerically similar for the 12.5 mg (low) dose and 25 mg (high) dose of aprocitentan.

See Sections 6.1 and 6.3 for additional analyses and discussion regarding treatment effects on blood pressure for the 12.5 mg and 25 mg doses of aprocitentan.

Table 11. Primary Analysis Results: Change From Baseline in SiSBP (mmHg) at Week 4, FAS

Parameter	Statistic	Aprocitentan	Aprocitentan	Placebo
		12.5 mg N=243	25 mg N=243	
Baseline	#Obs, n (%)	243 (100)	244 (100)	244 (100)
	Mean SiSBP (SD)	153.2 (8.8)	153.3 (9.0)	153.3 (9.0)
Week 4	#Obs, n (%)	223 (92)	231 (95)	224 (92)
	Mean SiSBP (SD)	138.0 (14.9)	138.0 (14.2)	141.8 (15.2)
Prespecified primary analysis ¹	LSM change from baseline in SiSBP (SE)	-15.3 (0.9)	-15.2 (0.9)	-11.5 (0.9)
	Difference to placebo in LSM (SE)	-3.8 (1.3)	-3.7 (1.3)	-
	97.5% CI	(-6.8, -0.8)	(-6.7, -0.8)	-
	p-value	0.0042	0.0046	-
FDA Recommended primary analysis ²	LSM change from baseline in SiSBP (SE)	-15.4 (0.9)	-15.2 (0.9)	-11.6 (0.9)
	Difference to placebo in LSM (SE)	-3.8 (1.3)	-3.7 (1.3)	-
	97.5% CI	(-6.8, -0.8)	(-6.6, -0.7)	-
	p-value	0.0043	0.0054	-

Source: Statistical reviewer's analysis; adsl.xpt, adbascosco.xpt

¹ The prespecified primary analysis used a treatment policy strategy for treatment discontinuation and rescue medication. Missing data were handled by MMRM and were not explicitly imputed.

² The FDA recommended primary analysis used a treatment policy strategy for treatment discontinuation and rescue medication. Missing data were imputed before fitting the model. See more details in "Missing data handling and FDA recommended primary analysis" subsection.

Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least squares mean; n, number of subjects in subset; N, overall number of subjects; #Obs, number of observations; SD, standard deviation; SE, standard error; SiSBP, sitting systolic blood pressure

Missing Data Handling and FDA Recommended Primary Analysis

Missing SiSBP data at baseline, Week 2 and Week 4 are shown in [Table 12](#) by treatment arm. No subjects had missing baseline values. In the overall study population, there were moderate missing rates for uAOBPM measurements at Week 2 and Week 4 (10% and 7%, respectively). A total of 20 (3%) subjects were missing data at both Week 2 and Week 4.

Table 12. Missing Primary Endpoint Data for Each Visit, Part 1, FAS

Visit	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=243	Placebo N=244	Total N=730
	n(%)	n(%)	n(%)	n(%)
Baseline	0 (0)	0 (0)	0 (0)	0 (0)
Week 2	28 (12)	20 (8)	24 (10)	72 (10)
Week 4	20 (8)	12 (5)	20 (8)	52 (7)
Both Week 2 and Week 4	6 (2)	6 (2)	8 (3)	20 (3)

Source: Statistical reviewer's analysis; adsl.xpt, adbasco.xpt

Abbreviations: FAS, full analysis set; n, number of subjects in subset; N, overall number of subjects

There are two concerns with how the prespecified primary analysis handled these missing data:

- 1) Since the missing data were handled directly by MMRM, the 20 (3%) subjects missing both Week 2 and Week 4 data were not included in the primary analyses given that no postbaseline data were collected. This violates the ITT principle and could potentially introduce bias even though the impact might be small given the low missing rate (3%).
- 2) For subjects that were included in the MMRM model, all the missing data were imputed under the MAR assumption, which is not the approach recommended by the FDA. During product development, FDA had indicated to the Applicant that “MMRM assumes the data missing at random (MAR). Subjects who receive rescue medication, prematurely discontinue treatment or withdraw from the study are likely to be different from those who remain in the study on treatment.”

To further explore and address the above missing data issues, subjects in the FAS were divided into four groups based on their missing data status after treatment discontinuation:

- Group a: Subjects who completed study treatment through Part 1 and completed study in Part 1 with available primary endpoint data.
- Group b: Subjects who did not complete study treatment through Part 1 but completed study in Part 1 with available primary endpoint data, i.e., retrieved dropouts.
- Group c: Subjects who completed study treatment through Part 1, but with missing primary endpoint data.
- Group d: Others, i.e., subjects who did not complete study treatment through Part 1 and with missing primary endpoint data, or subjects who discontinued study in Part 1.

A summary for subjects by their missing data status are shown in [Table 13](#).

Table 13. Summary for Subjects by Missing Data Status at Week 4 for Part 1, FAS

Subject Groups by Treatment Completion and Week 4 Missing Data Status	Completed Treatment in Part 1?	Have Observed In-Window Week 4 Data?	Aprocitentan 12.5 mg N=243 n(%)	Aprocitentan 25 mg N=243 n(%)	Placebo N=244 n(%)	Total N=730 n(%)
Group a	Yes	Yes	220 (90.5)	224 (92.2)	223 (91.4)	667 (91.4)
Group b (retrieved dropouts)	No	Yes	3 (1.2)	7 (2.9)	1 (0.4)	11 (1.5)
Group c	Yes	No	12 (4.9)	10 (4.1)	15 (6.1)	37 (5.1)
Group d	No	No	8 (3.3)	2 (0.8)	5 (2.0)	15 (2.1)

Source: Statistical reviewer's analysis; adsl.xpt, adbasc0.xpt

Abbreviations: FAS, full analysis set; n, number of subjects in subset; N, overall number of subjects

In principle, a retrieved dropout multiple imputation is preferred to handle missing data due to loss of follow-up and study withdrawal. However, according to [Table 13](#), there were not enough retrieved dropout subjects to support a reliable retrieved dropout multiple imputation ([Table 13](#)). After further consideration, the statistical team concluded that missing data should be handled in the primary analysis using a mixture of jump to reference multiple imputation based on MNAR and standard multiple imputation based on MAR. Specifically, under the treatment policy strategy to handle intercurrent events as specified in the SAP, missing primary endpoint data for subjects in group 1c were imputed based on subjects in group 1a with standard multiple imputation (MAR assumption) and missing data in group 1d were imputed with jump to reference multiple imputation. This approach follows the ITT principle by including all randomized subjects and handles missing data more appropriately when the missing data assumptions are unverifiable. Similar results were obtained as compared to the prespecified primary analysis.

Sensitivity Analyses

To further assess the robustness of the primary analysis results to missing data imputation assumptions, the scientific misconduct reported at study Site 4204, and intercurrent event handling, the following sensitivity analyses were conducted.

- For the reference-based multiple imputation approaches, copy reference and jump to reference multiple imputations were performed respectively. As opposed to the primary analysis, all subjects were included in the MMRM.
- For Site 4204, scientific misconduct, which led to subject participation in 2 clinical studies concurrently and serious violation of ALCOA+ (Principles of data integrity: attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available) requirements for study site study documentation was identified. Therefore, a sensitivity analysis was conducted excluding all 27 randomized subjects from Site 4204.
- Since the primary analysis used a treatment policy strategy for treatment discontinuation and rescue medication, a supplementary analysis was performed using a hypothetical strategy for rescue medication, in which any data after the intercurrent event of rescue medication were ignored and then imputed using jump to reference multiple imputation.

Results of the sensitivity/supplementary analyses showed similar treatment effects as compared to the primary analyses, and the p-values are all smaller than 0.025, indicating that the primary analyses results are robust ([Table 14](#)).

Table 14. Sensitivity Analyses for Primary Endpoint: Change From Baseline in SiSBP (mmHg) at Week 4, Part 1, FAS

Parameter	Aprocitentan 12.5 mg		Aprocitentan 25 mg	
	LSM	p-value	LSM	p-value
Primary analysis	-3.8	0.0042	-3.7	0.0046
Sensitivity/supplementary analysis				
Copy reference MI	-3.6	0.0072	-3.7	0.0056
Jump to reference MI	-3.6	0.0062	-3.5	0.0076
Excluding Site 4204	-3.3	0.0152	-4.2	0.0018
Hypothetical strategy	-3.3	0.0136	-3.3	0.0136

Source: Statistical reviewer's analysis; adsl.xpt, adbasc0.xpt

Abbreviations: FAS, full analysis set, LSM, least squares mean, MI, multiple imputation; SiSBP, sitting systolic blood pressure

Subgroup Analyses

Subgroups analyses were conducted using the same model as used in the primary analyses. Treatment effects were consistent across prespecified subgroups for both dose arms, except for the UACR and CKD subgroups, for which interaction p-values indicated potential heterogeneity (interaction p-value of 0.0011 and 0.0019, respectively) ([Figure 4](#) and [Figure 5](#)).

For baseline UACR categories (<30 mg/g, 30-300 mg/g, >300 mg/g), the estimated treatment effects for the UACR <30 mg/g subgroup and UACR =30-300 mg/g subgroup were similar to the overall treatment effects for both doses, while the estimated treatment effect for the UACR >300 mg/g subgroup appeared to be larger with wider confidence interval, visually deviating from the other two subgroups for both doses relative to placebo. Given the small sample size of the UACR >300 subgroup and that the treatment effect favored aprocitentan ([Table 9](#)), no further analyses were warranted.

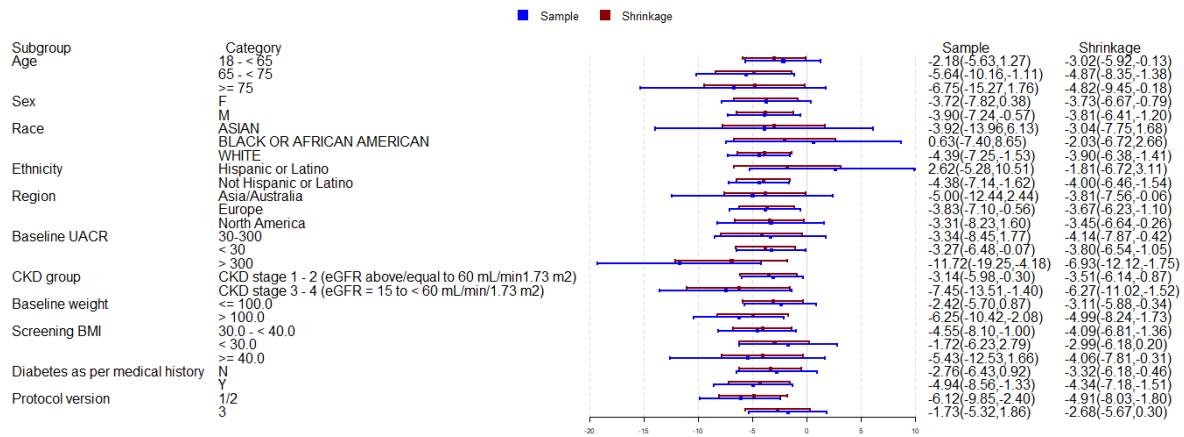
For baseline eGFR categories the estimated treatment effect appeared to be smaller than the overall treatment effect in subjects with eGFR ≥60 mL/min /1.73 m² and greater than the overall treatment effect in subjects with eGFR 15-60 mL/min /1.73 m². This finding was particularly notable for the 25 mg dose of aprocitentan, i.e., the confidence intervals of the treatment effects for the two CKD subgroups did not overlap and the estimated treatment effect for the subgroup with eGFR ≥60 mL/min /1.73 m² was much smaller (LSM difference = -1.26) than the overall treatment effect. Additional subgroup analyses were conducted for baseline eGFR categories using different blood pressure endpoints (including uAOBPM SiDBP, 24h ABPM SiSBP and SiDBP) in Part 1 and data from Part 3. The results (see [Section 16](#)) suggest that the findings for the primary efficacy endpoint in eGFR subgroups may be due to chance and not reflect a true difference.

Shrinkage Estimates

There are typically some random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical

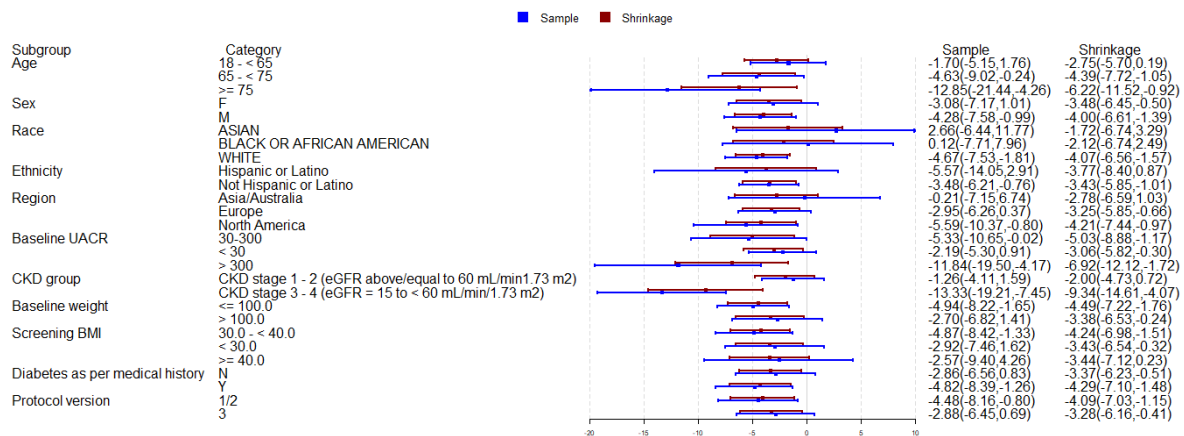
model based on summary sample estimates. This approach leads to improved precision and lower variability, shown with narrower confidence intervals, most notably in subgroups with a smaller sample size. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in the underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a “weighted” average of the sample estimate and overall estimate. A set of fairly noninfluential priors [$\mu \sim \text{Normal}(0, 10^2)$, $\tau^2 \sim \text{HalfNormal}(0, 10^2)$ with lower limit of 10^{-12}] were used to derive shrinkage estimates for all subgroups. These results showed narrower confidence intervals and more consistent results across different subgroups.

Figure 4. Subgroup Analyses, Aprocitentan 12.5 mg vs. Placebo, Part 1



Source: Statistical reviewer’s analysis; adsl.xpt, adbasc0.xpt
Treatment effects and corresponding confidence intervals are shown in the center of the plot.
The subgroup analyses used the same MMRM as was used for the primary analysis.
Abbreviations: BMI, body mass index, CKD, chronic kidney disease, DB, double-blind, eGFR, estimated glomerular filtration rate, F, female; M, male, MMRM, mixed models for repeated measures N, no; UACR, urine albumin-to-creatinine ratio; vs., versus; Y, yes

Figure 5. Subgroup Analyses, Aprocitentan 25 mg vs. Placebo, Part 1



Source: Statistical reviewer’s analysis; adsl.xpt, adbasc0.xpt
Treatment effects and corresponding confidence intervals are shown in the center of the plot.
The subgroup analyses used the same MMRM as was used for the primary analysis.
Abbreviations: BMI, body mass index, CKD, chronic kidney disease, DB, double-blind, eGFR, estimated glomerular filtration rate, F, female; M, male, MMRM, mixed models for repeated measures N, no; UACR, urine albumin-to-creatinine ratio; vs., versus; Y, yes

Additional Analysis for Black or African American Subgroup

Although the interaction p-value for the race variable did not suggest heterogeneity among race subgroups, the subgroup analyses showed neutral treatment effects for Black or African American subjects for both aprocitentan 12.5 mg and 25 mg ([Table 15](#)).

Table 15. Change From Baseline in SiSBP (mmHg) at Week 4 for Race Subgroup, FAS

Parameter	Statistic	Aprocitentan	Aprocitentan	Placebo
		12.5 mg N=243	25 mg N=243	
Primary analysis	N (%)	223 (92)	231 (95)	224 (92)
	LSM change from baseline in SiSBP (SE)	-15.3 (0.9)	-15.2 (0.9)	-11.5 (0.9)
	Difference to placebo in LSM (SE)	-3.8 (1.3)	-3.7 (1.3)	-
Race subgroup analysis interaction p-value=0.4566				
Black or AA subgroup	n	27	28	23
	LSM change from baseline in SiSBP (SE)	-11.3 (2.7)	-11.8 (2.6)	-12.0 (2.9)
	Difference to placebo in LSM (SE)	0.6 (4.0)	0.1 (3.9)	-
White subgroup	n	186	188	186
	LSM change from baseline in SiSBP (SE)	-15.6 (1.0)	-15.9 (1.0)	-11.2 (1.0)
	Difference to placebo in LSM (SE)	-4.4 (1.5)	-4.7 (1.5)	-
Asian subgroup	n	10	14	13
	LSM change from baseline in SiSBP (SE)	-19.2 (3.6)	-12.6 (3.0)	-15.3 (3.2)
	Difference to placebo in LSM (SE)	-3.9 (4.9)	2.7 (4.5)	-

Source: Statistical reviewer's analysis; adsl.xpt, adbasco.xpt

Abbreviations: AA, African American; FAS, full analysis set; LSM, least squares mean; n, number of subjects in subset; N, overall number of subjects; SE, standard error; SiSBP, sitting systolic blood pressure

Further analyses were conducted using different blood pressure endpoints in Part 1 and data from Part 3. As shown in [Table 16](#), these analyses did not suggest a smaller treatment effect in the subgroup of subjects who were Black or African American. These analyses indicate that the neutral treatment effect observed in the forest plots for the primary endpoint for the Black or African American subgroup was likely due to randomness given the small sample size.

Table 16. Additional Analyses for Black or AA Subgroup

Parameter (mmHg)	Statistic	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
<i>DB Part 1, FAS</i>				
	N	243	243	244
Week 4	n, AA group, FAS	28	28	26
SiSBP	LSM change from DB baseline in SiSBP (SE)	-11.3 (2.7)	-11.8 (2.6)	-12.0 (2.9)
	Difference to placebo in LSM (SE)	0.63 (4.0)	0.12 (3.9)	-
SiDBP	LSM change from DB baseline in SiDBP (SE)	-9.22 (1.7)	-9.56 (1.6)	-7.16 (1.8)
	Difference to placebo in LSM (SE)	-2.06 (2.4)	-2.40 (2.4)	-
24-hour ABPM SiSBP	LSM change from DB baseline in 24 ABPM SiSBP (SE)	-3.97(2.2)	-8.58 (2.2)	-0.74 (2.4)
	Difference to placebo in LSM (SE)	-3.23 (3.3)	-7.85 (3.2)	-
24-hour ABPM SiDBP	LSM change from DB baseline in 24 ABPM SiDBP (SE)	-4.02 (1.5)	-6.78 (1.5)	-2.70 (1.6)
	Difference to placebo in LSM (SE)	-1.32 (2.2)	-4.07 (2.2)	-
<i>Part 3, mFAS</i>				
	N	-	307	307
Week 40	n, AA group, mFAS	-	30	36
SiSBP	LSM change from DB-WD baseline in SiSBP (SE)	-	-3.26 (2.4)	6.61 (2)
	Difference to placebo in LSM (SE)	-	-9.87 (3.1)	-
SiDBP	LSM change from DB-WD baseline in SiDBP (SE)	-	-2.42 (2.0)	6.57 (1.7)
	Difference to placebo in LSM (SE)	-	-8.99 (2.6)	-
24-hour ABPM	LSM change from DB-WD baseline in 24 ABPM SiSBP (SE)	-	-0.62 (2.6)	7.51 (2.6)
	Difference to placebo in LSM (SE)	-	-8.13 (3.6)	-
24-hour ABPM	LSM change from DB-WD baseline in 24 ABPM SiDBP (SE)	-	0.67 (1.8)	7.92 (1.8)
	Difference to placebo in LSM (SE)	-	-7.25 (2.5)	-

Source: Statistical reviewer's analysis; adsl.xpt, adbascosco.xpt, adbascosvo.xpt

Abbreviations: AA, African American; ABPM, ambulatory blood pressure monitoring; DB, double-blind; FAS, full analysis set; LSM, least squares mean; mFAS, modified full analysis set; n, number of subjects in subset; N, overall number of subjects; SE, standard error; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Summary of Findings in Part 1

Part 1 assessed the efficacy of two doses of aprocitentan in reducing SiSBP using uAOBPM obtained at trough. Both doses were statistically superior to placebo in reducing SiSBP at Week 4. The size of the placebo-corrected treatment effect, which was similar in the 12.5 mg and 25 mg dose arms (a reduction of 3.8 mmHg and 3.7 mmHg, respectively), is considered clinically meaningful. Sensitivity analyses confirmed the robustness of the primary analysis results. For the most part, treatment effects were consistent across prespecified subgroups for both dose arms for the prespecified primary endpoint. However, for the UACR and eGFR subgroups, interaction p-values indicated potential heterogeneity. In addition, although the interaction p-value for the race variable did not suggest heterogeneity among race subgroups, the subgroup analyses showed neutral effects for Black or African American subjects for both aprocitentan 12.5 mg and 25 mg. Further analyses were conducted to explore these findings. These additional analyses suggested that the extreme large or small treatment effects observed in these subgroups were due to small sample sizes and randomness.

Results of Part 3

Part 3 of the study consisted of a 12-week double-blind period in which subjects were rerandomized to placebo or remained on aprocitentan. Subjects that completed treatment through Parts 1 and 2 were then rerandomized to aprocitentan 25 mg or placebo in Part 3. Of the 730 subjects randomized in Part 1, there were 614 subjects randomized to Part 3. This is more than the planned sample size of 380, the Applicant stated that the larger-than-planned sample size was caused by the addition of sites and countries in 2020. These additional sites and countries were meant to compensate for the lower recruitment due to the Covid-19 pandemic..

Demographic

Baseline demographics for Part 3 were generally balanced among the treatment arms ([Table 17](#)). A greater proportion of subjects <65 years of age were randomized to the placebo group; however, the mean and median age was similar in the two arms. Overall, the demographics of the subjects who were rerandomized in Part 3 were similar to those of subjects in Part 1 ([Table 8](#)).

Table 17. Baseline Demographics, Part 3, mFAS

Parameter	Aprocitentan	Placebo N=307	Total N=614
	25 mg N=307		
Age, years			
Mean (SD)	62.2 (10.52)	60.8 (10.65)	61.5 (10.60)
Median	64.0	62.0	62.5
IQR	55.0, 69.0	53.0, 69.0	55.0, 69.0
Min, max	24.0, 84.0	30.0, 83.0	24.0, 84.0
Age, years, n (%)			
18 to <65	160 (52.1)	189 (61.6)	349 (56.8)
65 to <75	114 (37.1)	90 (29.3)	204 (33.2)
≥75	33 (10.7)	28 (9.1)	61 (9.9)

Parameter	Aprocitentan 25 mg N=307	Placebo N=307	Total N=614
Sex, n (%)			
Female	124 (40.4)	122 (39.7)	246 (40.1)
Male	183 (59.6)	185 (60.3)	368 (59.9)
Race, n (%)			
Asian	16 (5.2)	14 (4.6)	30 (4.9)
Black or African American	30 (9.8)	36 (11.7)	66 (10.7)
White	259 (84.4)	256 (83.4)	515 (83.9)
Missing	2 (<1)	1 (<1)	3 (<1)
Ethnicity, n (%)			
Hispanic or Latino	28 (9.1)	26 (8.5)	54 (8.8)
Not Hispanic or Latino	276 (89.9)	279 (90.9)	555 (90.4)
Missing	3 (1.0)	2 (<1)	5 (<1)
Region, n (%)			
Asia/Australia	21 (6.8)	21 (6.8)	42 (6.8)
Europe	205 (66.8)	190 (61.9)	395 (64.3)
North America	81 (26.4)	96 (31.3)	177 (28.8)
BMI (kg/m ²) at screening			
Mean (SD)	33.4 (6.50)	33.9 (5.88)	33.6 (6.20)
Median	32.4	33.3	32.8
IQR	28.4, 37.8	29.6, 37.1	29.2, 37.6
Min, max	19.4, 58.8	22.7, 63.9	19.4, 63.9
BMI (kg/m ²) groups, n (%)			
25 to <30	82 (26.7)	79 (25.7)	161 (26.2)
30 to <40	152 (49.5)	180 (58.6)	332 (54.1)
<25	24 (7.8)	8 (2.6)	32 (5.2)
≥40	49 (16.0)	40 (13.0)	89 (14.5)

Source: Statistical reviewer's analysis; adsl.xpt

Abbreviations: BMI, body mass index; IQR, interquartile range; max, maximum; mFAS, modified full analysis set; min, minimum; n, number of subjects in subset; N, overall number of subjects; SD, standard deviation

Baseline Disease Characteristics

Baseline disease characteristics were generally balanced across treatment groups in Part 3 and were similar to Part 1 ([Table 9](#)).

Table 18. Baseline Disease Characteristics, Part 3, mFAS

Parameter	Aprocitentan 25 mg N=307	Placebo N=307	Total N=614
Time from first diagnosis of hypertension to screening (years)			
Mean (SD)	17.0 (10.80)	16.2 (10.11)	16.6 (10.46)
Median	15.9	15.0	15.4
IQR	8.8, 22.0	9.3, 21.8	8.9, 21.8
Min, max	0.1, 64.9	0.0, 50.8	0.0, 64.9
Missing	1	0	1
SiSBP (mmHg) at screening			
Mean (SD)	156.1 (11.37)	157.3 (12.13)	156.7 (11.76)
Median	155.0	155.0	155.0
IQR	148.0, 163.5	148.0, 166.0	148.0, 165.0
Min, max	120.0, 202.0	126.0, 210.0	120.0, 210.0
Missing	3	2	5

Parameter	Aprocitentan		Total N=614
	25 mg N=307	Placebo N=307	
SiDBP (mmHg) at screening			
Mean (SD)	88.6 (10.35)	88.5 (10.61)	88.6 (10.48)
Median	88.0	88.0	88.0
IQR	81.5, 95.0	81.0, 97.0	81.0, 96.0
Min, max	64.0, 131.0	63.0, 130.0	63.0, 131.0
Missing	3	2	5
UACR (mg/g) category, n (%)			
30-300	71 (23.1)	67 (21.8)	138 (22.5)
<30	190 (61.9)	209 (68.1)	399 (65.0)
>300	40 (13.0)	29 (9.4)	69 (11.2)
Missing	6 (2.0)	2 (<1)	8 (1.3)
eGFR (ml/min/1.73m ²) category, n (%)			
30 to <45	20 (6.5)	15 (4.9)	35 (5.7)
45 to <60	42 (13.7)	31 (10.1)	73 (11.9)
<30	6 (2.0)	5 (1.6)	11 (1.8)
≥60	239 (77.9)	256 (83.4)	495 (80.6)

Source: Statistical reviewer's analysis; adbasco.xpt

Abbreviations: IQR, interquartile range; max, maximum; mFAS, modified full analysis set; min, minimum; n, number of subjects in subset; N, overall number of subjects SD, standard deviation; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure; UACR, urine albumin-to-creatinine ratio

Part 3 Disposition

Of the 614 rerandomized subjects, 36 (6%) discontinued study drug during Part 3, and 22 (3.6%) discontinued the study ([Table 19](#)). The most frequently reported reasons for treatment discontinuation were adverse event [15 (2.4%)] and “other” [15 (2.4%)]. There was one death in the aprocitentan 25 mg group due to multiple organ dysfunction syndrome after the Week 40 analysis visit.

Table 19. Disposition, Part 3, mFAS

Parameter	Aprocitentan		Total N=614 n(%)
	25 mg N=307 n(%)	Placebo N=307 n(%)	
Rerandomized	307 (100)	307 (100)	614 (100)
Discontinued study drug	18 (5.9)	18 (5.9)	36 (5.9)
Adverse event	8(2.6)	7(2.3)	15(2.4)
Withdrawal by subject	1(0.3)	4(1.3)	5(0.8)
Lost to follow-up	0(0.0)	1(0.3)	1(0.2)
Other	9(2.9)	6(2.0)	15(2.4)
Discontinued study	11 (3.6)	11 (3.6)	22 (3.6)
Withdrawal by subject	3 (1)	4 (1.3)	7 (1.1)
Death	1 (0.3)	0 (0)	1 (0.2)
Lost to follow-up	0 (0)	1 (0.3)	1 (0.2)
Adverse event	0 (0)	2 (0.7)	2 (0.3)
Other	7 (2.3)	4 (1.3)	11 (1.8)

Source: Statistical reviewer's analysis; adsl.xpt

Abbreviations: mFAS, modified full analysis set, n, number of subjects in subset; N, overall number of subjects

Analyses for the Secondary Endpoint

The secondary endpoint of change in SiSBP from DB-WD baseline (Week 36) to Week 40 was analyzed using an MMRM analysis. The results of the prespecified secondary analysis and the FDA recommended analysis (see “Missing Data Handling and FDA Recommended Primary Analysis” for further details) are shown in [Table 20](#). Statistical significance was demonstrated in both analyses and both approaches resulted in a similar estimate of the treatment effect [LSM difference: -5.7 mmHg; 95% CI: -7.8, -3.6; p-value<0.0001 based on the FDA recommended analysis].

Table 20. Secondary Analysis Result: Change From DB-WD Baseline in SiSBP (mmHg) at Week 40, mFAS

Parameter	Statistic	Aprocitentan	
		25 mg N=307	Placebo N=307
DB-WD baseline	#Obs, n (%)	307 (100)	307 (100)
	Mean SiSBP (SD)	135.3 (15.6)	136.4 (14.8)
Week 40	#Obs, n (%)	261 (85)	267 (87)
	Mean SiSBP (SD)	134.0 (15.3)	140.5 (16.7)
Prespecified secondary analysis ¹	LSM change from DB-WD baseline in SiSBP (SE)	-1.5 (0.8)	4.4 (0.8)
	Difference to placebo in LSM (SE)	-5.8 (1.1)	
	95% CI	(-8.2, -3.4)	
	p-value	<.0001	
FDA-recommended secondary analysis ²	LSM change from DB-WD baseline in SiSBP (SE)	-1.5 (0.8)	4.3 (0.8)
	Difference to placebo in LSM (SE)	-5.7 (1.1)	
	95% CI	(-7.8, -3.6)	
	p-value	<.0001	

Source: Statistical reviewer’s analysis; adsl.xpt, adbasc0.xpt

¹ The prespecified secondary analysis used a treatment policy strategy for treatment discontinuation and rescue medication. Missing data were handled by MMRM and were not explicitly imputed.

² The FDA recommended secondary analysis used a treatment policy strategy for treatment discontinuation and rescue medication. Missing data were imputed before fitting the model. For further details, see “Missing data handling and FDA recommended secondary analysis” subsection.

Abbreviations: CI, confidence interval; DB-WD, double-blind withdrawal; LSM, least squares mean; mFAS, modified full analysis set; MMRM, mixed-model repeated measures; #Obs, number of observations; SE, standard error; SiSBP, sitting systolic blood pressure

Missing Data Handling and FDA Recommended Secondary Analysis

Similar to the primary endpoint analysis, missing data were handled by MMRM in the prespecified main analysis of the secondary endpoint and assumed to be missing at random. At Week 40, 46 (15%) and 40 (13%) subjects were missing SiSBP measurements in the aprocitentan 25 mg group and placebo group, respectively, resulting in a 14% overall missing rate for Week 40 ([Table 21](#)). There were 22 subjects (4%) missing both Week 38 and Week 40 data. These 22 subjects were not included in the MMRM analysis for the secondary efficacy endpoint, raising the same concerns as those discussed for the primary analysis. As such, the FDA conducted an alternative analysis using similar methods as those used in the FDA analysis of the primary endpoint (i.e., a mixture of standard MI and J2R-MI) to obtain an estimate of the treatment effect in Part 3 that more appropriately handles missing data (see [Table 20](#)).

Table 21. Missing Secondary Endpoint Data for Each Visit, Part 3, mFAS

Visit	Aprocitentan 25 mg	Placebo	Total
	N=307 n (%)	N=307 n (%)	N=614 n (%)
DB-WD baseline	0 (0)	0 (0)	0 (0)
Week 38	82 (27)	55 (18)	137 (22)
Week 40			
Actual visits	46 (15)	40 (13)	86 (14)
Visits scheduled as per protocol	11 (4)	21 (7)	32 (5)
Both Week 38 and Week 40	9 (3)	13 (4)	22 (4)
Week 44	14 (5)	23 (7)	37 (6)
Week 48	34 (11)	23 (7)	57 (9)

Source: Statistical reviewer's analysis; adsl.xpt, adbasco.xpt
Abbreviations: DB-WD, double-blind withdrawal; mFAS, modified full analysis set; n, number of subjects in subset; N, overall number of subjects

Sensitivity analyses similar to those performed for the primary endpoint were also performed for the secondary endpoint (change in SiSBP from DB-WD baseline (Week 36) to Week 40). One additional sensitivity analysis was performed because of the high missing rate at Week 40. The main reason for the high missing rate (14%) at Week 40 was that 62 subjects performed the Week 40 visits outside of the Week 40 analysis window (Day 21 to Day 41 after rerandomization). The main analysis used actual analysis visits and considered these Week 40 visits as missing. Thus, a supplementary analysis was performed based on visits as per protocol (not analysis windows).

The results of these sensitivity analyses are shown in [Table 22](#). As shown in the table, the LSM differences for all of the sensitivity/supplementary analyses (as well as the main analysis result in [Table 20](#)) were larger than the LSM differences seen in Part 1. Because the actual sample size of 614 was much larger than the planned sample size of 380, the study was overpowered to detect aprocitentan's effect on blood pressure during the randomized withdrawal phase of the trial (assumed in power calculations to be 5 mmHg), which likely contributed to the high statistical significance of the p-values shown in the table. However, given that the estimated treatment effect during the randomized withdrawal phase was larger than in Part 1, as well as the results of the sensitivity/supplementary analyses, the secondary endpoint findings are considered to be robust and to support the conclusion that aprocitentan's blood pressure lowering effect is durable.

Table 22. Sensitivity Analyses for Secondary Endpoint: Change From DB-WD Baseline in SiSBP (mmHg) at Week 40, Part 3, mFAS

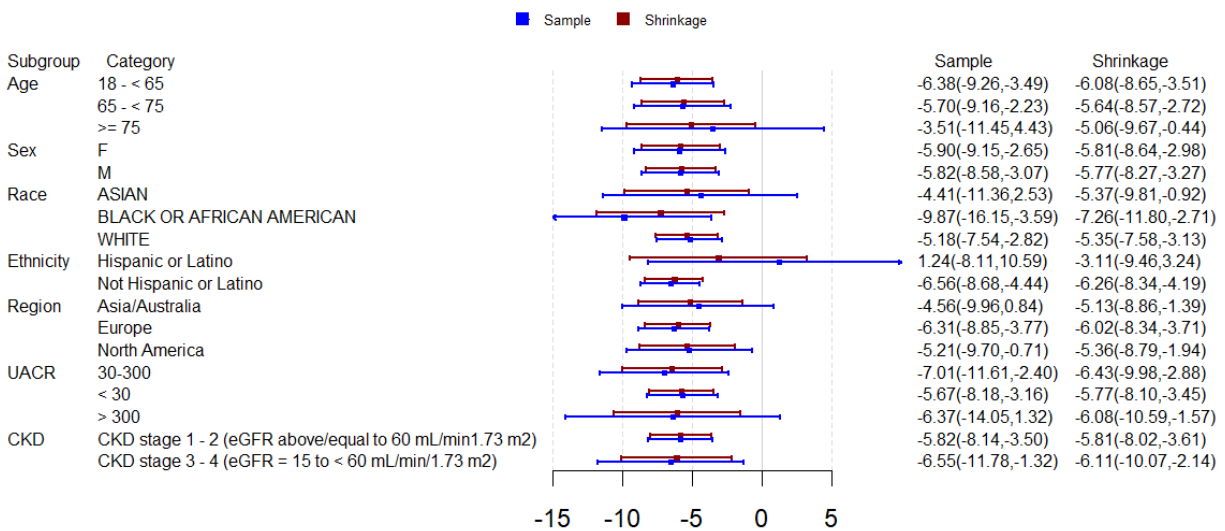
Parameter	LSM Difference (SE)	p-Value
Secondary analysis	-5.8 (1.08)	<0.0001
Sensitivity/supplementary Analysis		
Copy reference MI	-5.4 (1.09)	<0.0001
Jump to reference MI	-4.8 (1.09)	<0.0001
Excluding Site 4204	-5.9 (1.09)	<0.0001
Hypothetical Strategy	-5.0 (1.10)	<0.0001
Using visits per protocol	-6.6 (1.05)	<0.0001

Source: Statistical reviewer's analysis; adsl.xpt, adbasco.xpt
Abbreviations: DB-WD, double-blind withdrawal; mFAS, modified full analysis set; SE, standard error; SiSBP, sitting systolic blood pressure

Subgroup Analyses

Subgroup analyses, including shrinkage analyses (where the same set of noninfluential priors as for the subgroup analyses of primary endpoint were used), were also performed for the secondary endpoint. Overall, the treatment effects were consistent across subgroups for the secondary endpoint (Figure 6). The Hispanic or Latino subgroup showed a treatment effect in the unfavorable direction, however, given the small sample size (and thus wide confidence interval) of this subgroup and the large treatment effect shown in Part 1 for aprocitentan 25 mg versus placebo, it is likely that this unfavorable effect is not a real finding and reflects a random low value.

Figure 6. Subgroup Analyses for Secondary Endpoint, Part 3



Source: Statistical reviewer's analysis; adsl.xpt, adbasc0.xpt
 Treatment effects and corresponding confidence intervals are shown in the center of the plot.
 The subgroup analyses used the same MMRM as was used for the primary analysis.
 Abbreviations: CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate, F, female; M, male, MMRM, mixed models for repeated measures UACR, urine albumin-to-creatinine ratio; vs., versus

Summary of Findings in Part 3

The persistence of the BP-lowering effect of aprocitentan was demonstrated in Part 3 of the study, with increased mean SiSBP in subjects rerandomized to placebo, and maintained mean SiSBP in subjects rerandomized to aprocitentan 25 mg. The robustness of the main analysis was supported by the sensitivity analyses. Subgroup findings were, as a whole, consistent with the findings in the overall population.

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7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies, including safety pharmacology studies, general toxicology studies, a full battery of genetic toxicology studies, and a partial battery of developmental and reproductive toxicology studies were conducted with aprocitentan. The Applicant also provided a letter of authorization referencing relevant data submitted to NDA 214410 for macitentan. Key information on the reproductive safety of aprocitentan was provided by the developmental and reproductive toxicology studies conducted previously with macitentan. Similarly, the carcinogenicity assessment for aprocitentan was based on studies conducted with macitentan. This approach was previously agreed upon between the Applicant and the Agency since

aprocitentan is a major active metabolite of macitentan and represents 50% and approximately 90% of the combined exposure to macitentan and aprocitentan in rats and rabbits, respectively.

The key safety findings from nonclinical studies and their potential clinical relevance are discussed below. The exposure multiples in the discussion that follows were calculated based on the AUC (34.8 µg.hr/mL) at the maximum recommended human dose (MRHD) of 12.5 mg/day. For a more detailed summary of nonclinical study, refer to Section [13](#).

Embryo-Fetal Toxicities

In embryo-fetal developmental (EFD) toxicity studies, treatment with macitentan (for which aprocitentan is a major metabolite) in pregnant rats and rabbits revealed teratogenicity and developmental toxicity at all doses tested, and therefore a no observed adverse effect level (NOAEL) for embryo fetal toxicity in the rat and rabbits could not be established. These findings were consistent with findings with other members of the ERA class. The relevant animal data are summarized below.

- In pregnant rats, oral administration of 3, 10, and 150 mg/kg/day macitentan during the period of major organogenesis resulted in fetal abnormalities, which included cardiovascular and mandibular arch fusion malformations, at all doses tested. The aprocitentan AUC at the lowest macitentan dose tested (3 mg/kg/day) was approximately equivalent to the clinical exposure at the MRHD of 12.5 mg/day, based on AUC.
- In pregnant rabbits, oral administration of 2.5, 12.5, and 25 mg/kg/day macitentan during the period of major organogenesis resulted in fetal abnormalities, which included cardiovascular and mandibular arch fusion malformations, at all doses tested. The aprocitentan exposure at lowest dose tested (2.5 mg/kg/day) was approximately 15-fold the clinical exposure at the MRHD, based on AUC.
- In a pre- and postnatal developmental study in female rats, oral administration of 10, 50 or 250 mg/kg/day macitentan during the pregnancy and the lactational periods reduced pup survival and impaired male fertility of offspring at all doses. The aprocitentan exposure at the lowest dose (10 mg/kg/day) was approximately 2-fold the clinical exposure at the MRHD, based on AUC.

Following submission of the aprocitentan NDA, the Applicant submitted additional EFD toxicity studies in which aprocitentan itself was administered to animals. No embryo-fetal toxicity was observed in the EFD studies with aprocitentan alone at 5-fold and 29-fold the human exposure at the MRHD in rats and rabbits, respectively. The highest dose of aprocitentan tested in the rat EFD study was too low to identify a lowest-observed adverse effect level, a critical attribute of an EFD study for a drug with a teratogenic mechanism of action. Indeed, the rat study tested doses only up to 5-fold the clinical exposure, based on AUC. The mechanism of action for ERAs is well established to be teratogenic in animals. In the absence of direct comparisons to other ERAs at their relevant clinical exposures, the available information is insufficient to conclude that (b) (4). In conclusion, without studies that produced exposures resulting in the expected embryo-fetal toxicities, and without inclusion of a macitentan (or other ERA) comparator, the available data are insufficient to characterize the embryofetal risk of aprocitentan. Therefore, the risk assessment based on the

studies conducted with macitentan continues to represent the most appropriate data for communicating the reproductive risk associated with aprocitentan. Reproductive risk could be reevaluated when adequately designed EFD studies with aprocitentan that include macitentan or other ERA as a comparator are provided by the Applicant.

Fertility

Male Fertility

In a fertility study in male rats given aprocitentan for 15 weeks (including 10-week pre-mating period, 2-week mating period and 3-week post-mating period) at doses up to 250 mg/kg/day (approximately 52-fold the exposure at the MRHD, based on AUC), no aprocitentan related effects on male gonadal function and mating behavior were observed. Likewise, no significant aprocitentan-related adverse effects on reproductive endpoints, including testicular and epididymal sperm count, sperm motility or morphology parameters, were observed. Minimal dilation of the seminiferous tubules, but not tubular degeneration or atrophy, was observed in the testes at ≥ 50 mg/kg/day, which represents approximately 13-fold the exposure at the MRHD based on AUC.

In the repeat-dose toxicology studies in male rats and dogs given aprocitentan for 26 weeks or 39 weeks, respectively, at doses up to 250 mg/kg/day, an increased incidence of tubular degeneration/atrophy was observed at 250 mg/kg/day in rats and at ≥ 25 mg/kg/day in dogs, representing approximately 41-fold and 53-fold, respectively, the exposure at the MRHD, based on AUC. The tubular findings in the testes were resolved at the end of the recovery period in both species. Reversible minimal dilation of seminiferous tubules of the testes were observed at doses ≥ 50 mg/kg/day in rats and ≥ 5 mg/kg/day in dogs. These findings were not associated with degeneration or atrophy and were not considered adverse. The NOAEL was thus established at 50 mg/kg/day in rats and 5 mg/kg/day in dogs, which represent approximately 14- and 11-fold, respectively, the exposure at the MRHD based on AUC.

In animal studies with several other ERAs, including bosentan, ambrisentan and macitentan ([Actelion Pharmaceuticals US 2001](#); [Gilead Sciences 2007](#); [Actelion Pharmaceuticals US 2013](#)), testicular tubular atrophy was observed in rodents, similar to what was observed with aprocitentan. Adverse effects on sperm count and male fertility were reported in rats treated with ambrisentan at high exposures, but similar findings were not reported with macitentan ([Gilead Sciences 2007](#); [Actelion Pharmaceuticals US 2013](#)). Decreased sperm counts were reported in patients receiving bosentan ([Actelion Pharmaceuticals US 2001](#)), but clinical sperm evaluations are not available for ambrisentan and macitentan. Given that the testicular tubular degeneration/atrophy observed in rats and dogs treated with aprocitentan occurred at high exposures (>41 -fold of aprocitentan exposure at the MRHD) and were not seen at or below the tested doses that provided 14- or 11-fold aprocitentan exposure at the MRHD, the concern for potential clinical risk might typically be deemed to be low. However, given the clinical risk identified with bosentan, a potential for clinical fertility risk with aprocitentan in males cannot be excluded.

Female Fertility

In a fertility and early embryonic development study in female rats given aprocitentan prior to mating, no effect on gonadal function, mating behavior, or fertility index was observed at doses up to 250 mg/kg/day. A higher percentage of acyclic females or females with an increased mean estrus cycle length was observed at 250 mg/kg/day. Mean number of implantation sites and mean number of corpora lutea was slightly reduced at ≥ 50 mg/kg/day, which is approximately 23-fold the AUC at the MRHD for females, based on AUC. The NOAEL for all measured parameters was determined to be 10 mg/kg/day, which represents 5-fold the clinical exposure at the MRHD, based on AUC. Given that no impairment of fertility function was observed, these findings are deemed to have limited clinical relevance.

Other Target Organ Toxicity

General toxicity studies were conducted for durations up to 26 weeks in rats and 39 weeks in dogs. Target organs of toxicity and the clinical relevance of the findings are discussed below.

Liver

In the 26-week toxicity study rats, a dose-dependent increase in liver weight and increasing incidence/severity of centrilobular hepatocellular hypertrophy and centrilobular fatty change (with a dark-colored appearance upon gross examination) were observed, which is considered an adaptive response caused by increased microsomal cytochrome P450 enzyme induction. At 250 mg/kg/day, approximately 41-fold the AUC at the MRHD, a moderate hepatocellular vacuolar degeneration/necrosis in the hypertrophic hepatocytes with minimal multinucleated hepatocytes was observed. In the 39-week toxicity study in dogs, an increased incidence of hepatocellular hypertrophy was also observed at ≥ 25 mg/kg/day (approximately 53-fold the AUC at the MRHD). No degenerative changes were observed in dogs at any dose, including the 50 mg/kg/day high dose. No adverse liver changes were observed in rats and dogs at 50 mg/kg/day (approximately 14-fold the AUC at the MRHD) and 75/50 mg/kg/day (approximately 82-fold the AUC at the MRHD), respectively. Hepatotoxicity has been reported with other ERAs and was seen in clinical studies with aprocitentan.

Hematological Toxicity

Treatment-related, reversible decreases in hemoglobin, RBC, and hematocrit (packed cell volume) were observed in female dogs at 75/50 mg/kg/day without any hemolysis, myelosuppression, or reticulocytes changes. No hematological changes were observed at 25 mg/kg/day, which is approximately 53-fold the AUC at the MRHD. While the large exposure margins and reversibility typically indicate minimal human risk, anemia has been reported with other ERAs and was seen in clinical studies with aprocitentan.

Nasal Congestion

Reversible increases in the incidence/severity of nasal congestion associated minimal to moderate submucosal edema and Goblet cell proliferation were observed at ≥ 25 mg/kg/day in dogs. These doses represent ≥ 53 -fold the clinical exposure at the MRHD based on AUC. Nasal congestion was also noted in the clinical studies at supra-pharmacological doses (>25 mg/kg/day). Given the foregoing, the human risk is considered to be low.

Genetic Toxicology

There was no evidence of mutagenicity or clastogenicity for aprocitentan in a standard battery of tests that included in vitro bacterial reverse mutation and chromosomal aberration assays, and an in vivo rat micronucleus study.

Carcinogenicity

The carcinogenicity assessment of aprocitentan was based on carcinogenicity studies conducted with another ERA, macitentan, for which its major metabolite is aprocitentan. No carcinogenicity studies were conducted with aprocitentan alone. Two-year carcinogenicity studies with macitentan did not identify any carcinogenic potential at doses up to 100 mg/kg/day and 250 mg/kg/day in mice and rats, where aprocitentan exposures represented approximately 30-fold and 11-fold, respectively, the clinical aprocitentan exposure at the MRHD based on AUC.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Aprocitentan is an ERA. Risks described in labeling for approved ERAs include embryo-fetal toxicity, hepatotoxicity, pulmonary edema with pulmonary veno-occlusive disease, decreased sperm counts, decreases in hemoglobin and hematocrit, and fluid retention. To date, all ERAs have been approved with a risk evaluation and mitigation strategy (REMS) for embryo-fetal toxicity, and two of the ERAs, bosentan and sparsentan, also include risk mitigation for hepatotoxicity in the REMS.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Aprocitentan is neither approved nor marketed in the United States or worldwide.

7.4. FDA Approach to the Safety Review

The safety review included a review of data quality, as well as adverse events (AEs), laboratory data, and vital sign datasets. AEs were analyzed by the Medical Dictionary for Regulatory Activities (MedDRA) [version 24.1] preferred term and by pooling similar AEs (referred to as the MedDRA SMQ or Food and Drug Administration Medical Dictionary for Regulatory Activities query [FMQ]). The review team did not identify any major data quality or integrity issues that raised concern. No major issues were identified with respect to recording, coding, and categorizing AEs, and the translation of verbatim terms to MedDRA preferred terms for the AEs reported in PRECISION was found to be acceptable.

The FDA safety review focused on the data collected in the PRECISION study. PRECISION included three treatment periods (Part 1, 2, and 3) with differing designs and durations, thus, the three treatment periods were analyzed separately. Adverse events were collected up through the

safety follow-up period, which started on the day after the last dose of study treatment and ended with a safety follow-up visit 30–33 days later. Adverse events of special interest (AESIs) included treatment-emergent adverse events (TEAEs) suggestive of anemia, edema/fluid retention, decompensation of heart failure, and hepatic injury. Since the target population has multiple cardio-cerebrovascular risk factors, an additional safety topic of interest included treatment-emergent major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, and MACE-plus, defined as hospitalization for heart failure, which were adjudicated by an independent central adjudication committee (CAC).

Safety data for the initial treatment period (Part 1; 4-week placebo-controlled) are presented in the following sections. For AESIs and any TEAEs that warranted further evaluation, data from study Parts 2 and 3 are also presented if pertinent.

7.5. Adequacy of the Clinical Safety Database

In the PRECISION study safety population, 724 subjects received at least one dose of aprocitentan, and the mean duration of exposure was 36.6 weeks ([Table 24](#)). Total subject exposures were sufficient to assess the safety of aprocitentan for the proposed indication and dose.

Table 24. Duration of Exposure, Safety Population, PRECISION Study

Parameter ¹	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=713	Aprocitentan Any Dose ² N=724	Placebo ³ N=444
	n (%)	n (%)	n (%)	n (%)
Duration of treatment, weeks				
Mean (SD)	4.2 (0.8)	35.9 (11.1)	36.6 (12.1)	10.1 (4.7)
Median (Q1, Q3)	4 (4, 4.3)	36.1 (32, 44)	36.9 (32.6, 47.4)	11.6 (4.1, 12.9)
Min, Max	0.1, 9.7	0.1, 53.3	0.1, 55.9	0.6, 21.7
Total exposure (person years)	19	486	506	86

Parameter ¹	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=713 n (%)	Aprocitentan Any Dose ² N=724 n (%)	Placebo ³ N=444 n (%)
Subjects treated, by duration, n (%)				
≥2 weeks	239 (98.4)	698 (97.9)	710 (98.1)	439 (98.9)
≥4 weeks	191 (78.6)	687 (96.4)	699 (96.5)	397 (89.4)
≥12 weeks	0	661 (92.7)	667 (92.1)	171 (38.5)
≥24 weeks	0	633 (88.8)	635 (87.7)	0
≥36 weeks	0	391 (54.8)	461 (63.7)	0
≥48 weeks	0	50 (7.0)	99 (13.7)	0
≥52 weeks	0	1 (0.1)	5 (0.7)	0

Source: adex.xpt and adsl.xpt; Software: R

¹ Exposure is calculated as the total exposure to treatment regardless of study part. In Part 2, exposure duration was unable to be calculated for eight subjects, as they were lost to follow-up and no treatment end date was recorded. The subjects' IDs were (b) (6)

(b) (6). In Part 3, exposure duration was unable to be calculated for two subjects, as no treatment end date was recorded for either subject. One subject was lost to follow-up (b) (6), and one subject (b) (6) could not remember date of last intake of study drug.

² Aprocitentan Any Dose" includes all randomized subjects who received at least 1 dose of aprocitentan (12.5 mg or 25 mg) during Part 1, 2, or 3. For subjects who received 12.5 mg in Part 1 and 25 mg in Part 2 and potentially Part 3, the total exposure is added together.

³ Total exposure on placebo may not be continuous, as a subject may have been randomized to placebo in Part 1, received single-blind Part 2 aprocitentan 25 mg, and then rerandomized to placebo in Part 3.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Overview of Treatment-Emergent Adverse Events

In Part 1 of the PRECISION study, TEAEs and serious AEs (SAEs) were reported in a higher proportion of aprocitentan-treated subjects than placebo-treated (Table 25). AEs leading to permanent discontinuation were also reported in a slightly numerically greater proportion of aprocitentan- as compared to placebo-treated subjects. Although AEs leading to dose interruption were reported in a slightly numerically greater proportion of subjects in the aprocitentan 12.5 mg dose group as compared to placebo, a similar finding was not seen at the higher dose.

Table 25. Overview of Treatment-Emergent Adverse Events, Safety Population, Part 1, PRECISION Study

Event Category	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	SAE	8 (3.3)	8 (3.3)	3 (1.2)	2.1 (-0.6, 4.7)
SAEs with fatal outcome	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
AE leading to permanent discontinuation	7 (2.9)	5 (2.0)	2 (0.8)	2.1 (-0.3, 4.4)	1.2 (-0.9, 3.3)

Event Category	Aprocitentan	Aprocitentan	Placebo	Aprocitentan	Aprocitentan
	12.5 mg N=243 n (%)	25 mg N=245 n (%)		12.5 mg vs. Placebo Risk Difference (%) (95% CI)	25 mg vs. Placebo Risk Difference (%) (95% CI)
AE leading to dose modification	5 (2.1)	3 (1.2)	2 (0.8)	1.2 (-0.9, 3.3)	0.4 (-1.4, 2.2)
AE leading to interruption	5 (2.1)	3 (1.2)	2 (0.8)	1.2 (-0.9, 3.3)	0.4 (-1.4, 2.2)
AE leading to reduction	0	0	0	0 (0, 0)	0 (0, 0)
AE leading to dose delay	0	0	0	0 (0, 0)	0 (0, 0)
Other	0	0	0	0 (0, 0)	0 (0, 0)
Any AE	67 (27.6)	90 (36.7)	47 (19.4)	8.2 (0.6, 15.7)	17.3 (9.5, 25.1)
Severe	8 (3.3)	7 (2.9)	2 (0.8)	2.5 (-0.1, 5.0)	2.0 (-0.3, 4.4)
Moderate	24 (9.9)	27 (11.0)	15 (6.2)	3.7 (-1.1, 8.5)	4.8 (-0.1, 9.8)
Mild	35 (14.4)	56 (22.9)	30 (12.4)	2.0 (-4.1, 8.1)	10.5 (3.8, 17.2)

Source: adae.xpt; Software: R; MedDRA Version: 24.1

Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2).

Duration is median 4 weeks (minimum 0.1, maximum 9.7 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the Investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2. Deaths

There were 11 treatment-emergent deaths (1.3%) during the study, all reported in aprocitentan-treated subjects. Of these deaths, one was reported in Part 1, nine were reported during Part 2 and one was reported in Part 3 ([Table 26](#)). Five of the deaths were attributed to COVID-19 (Part 1, n=1; Part 2, n=3; Part 3, n=1), one death was attributed to a colon perforation from a colonoscopy (Part 2), and one death was attributed to invasive breast carcinoma (primary cause of death) with concurrent subdural hemorrhage and brain edema (Part 2). The remaining four deaths were adjudicated as MACE, all reported in Part 2 with no comparator arm. Based on a review of the cases as well as what is known about the pharmacologic class, it seems unlikely that aprocitentan played a role in these deaths. See Section [7.6.6](#) for further discussion of MACE. [Table 139](#) provides the listing of subject deaths; the narratives for the deaths adjudicated as MACE are provided in [Table 140](#).

Table 26. Treatment-Emergent Deaths¹ by Preferred Term, Safety Population, PRECISION Study

Study part (analysis set) Primary cause of death (Preferred Term)	Aprocitentan 12.5 mg	Aprocitentan 25 mg	Placebo
DB part 1 (SAF)	N = 243	N = 245	N = 242
	n (%)	n (%)	n (%)
Subjects who died	1 (0.4)	0	0
COVID-19 pneumonia	1 (0.4)	0	0
SB part 2 (rSAF)	Aprocitentan 25 mg		
	N = 704		
	n (%)		
Subjects who died	9 (1.3)		
COVID-19 pneumonia	3 (0.4)		
Cerebrovascular accident (M)	2 (0.3)		
Death (M)	1 (0.1)		
Invasive breast carcinoma ^a (M)	1 (0.1)		
Procedural intestinal perforation	1 (0.1)		
Sudden cardiac death (M)	1 (0.1)		
DB-WD part 3 (mSAF)	Aprocitentan 25 mg	Placebo	
	N = 310	N = 303	
	n (%)	n (%)	
Subjects who died	1 (0.3)	0	
Multiple organ dysfunction syndrome ^b	1 (0.3)	0	

Source: CSR for Trial ID-080A301: PRECISION, Table 12-11. MedDRA version 24.1; verified by FDA reviewer

¹ Treatment-emergent deaths are those that occurred during treatment up to 30 days after the last dose

^a Primary cause of death was reported as invasive breast carcinoma; the case was adjudicated as MACE due to the concurrent SAEs of brain edema and subdural hemorrhage.

^b Subject had concurrent SAE of COVID-19 pneumonia with fatal outcome.

Abbreviations: COVID-19, coronavirus disease 2019; CSR, clinical study report; DB, double-blind; DB-WD, double-blind withdrawal; M, MACE; MACE, major adverse cardiovascular event; mSAF, modified safety analysis set; N, number of subjects in treatment arm; n, number of subjects with at least one event; rSAF, restricted safety analysis set; SAE, serious adverse event; SAF, safety analysis set; SB, single-blind

7.6.3. Serious Treatment-Emergent Adverse Events

In Part 1 of PRECISION, SAEs were uncommon but reported in a slightly higher proportion of aprocitentan-treated subjects (3% in each dosing arm) as compared to placebo (1%). With the exception of the Thrombosis FMQ (narrow), the risk difference versus placebo was less than 1% for specific preferred terms or groupings (Table 27). For the Thrombosis FMQ, although the risk difference was 1.2% for the 12.5 mg arm, the risk difference was -0.4% for the 25 mg arm.

Table 27. Subjects With Serious Treatment-Emergent Adverse Events¹ by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, PRECISION Study, Part 1

System Organ Class (SOC) FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243	Aprocitentan 25 mg N=245	Placebo N=242	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	n (%)	n (%)	n (%)		
Subjects with at least 1 SAE	8 (3.3)	8 (3.3)	3 (1.2)	2.1 (-0.6, 4.7)	2.0 (-0.6, 4.7)
Cardiac disorders (SOC)					
Acute Coronary Syndrome (FMQ)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial Infarction (FMQ)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial Ischemia (FMQ)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Heart Failure (FMQ)	0	2 (0.8)	0	0 (0, 0)	0.8 (-0.3, 1.9)
Cardiac failure	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Cardiac failure chronic	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Pulmonary oedema	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Systemic Hypertension (FMQ)	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Blood pressure increased	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Gastrointestinal disorders (SOC)					
Pancreatitis (FMQ)	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Pancreatitis chronic	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
General disorders and administration site conditions (SOC)					
Dizziness (FMQ)	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Meniere's disease	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Peripheral Edema (FMQ)	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Oedema peripheral	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Hepatobiliary disorders (SOC)					
Cholecystitis (FMQ)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Cholecystitis acute	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Infections and infestations (SOC)					
Pneumonia (FMQ)	1 (0.4)	1 (0.4)	0	0.4 (-0.4, 1.2)	0.4 (-0.4, 1.2)
Pneumonia	1 (0.4)	1 (0.4)	0	0.4 (-0.4, 1.2)	0.4 (-0.4, 1.2)
Viral Infection (FMQ)	2 (0.8)	0	1 (0.4)	0.4 (-1.0, 1.8)	-0.4 (-1.2, 0.4)
COVID-19 pneumonia	2 (0.8)	0	1 (0.4)	0.4 (-1.0, 1.8)	-0.4 (-1.2, 0.4)
Purulent Material (FMQ)	0	1 (0.4)	1 (0.4)	-0.4 (-1.2, 0.4)	-0.0 (-1.1, 1.1)
Abscess jaw	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Peritonsillar abscess	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)

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System Organ Class (SOC)	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
FMQ (Narrow)					
Preferred Term					
Bacterial Infection (FMQ)	1 (0.4)	3 (1.2)	2 (0.8)	-0.4 (-1.8, 1.0)	0.4 (-1.4, 2.2)
Cholecystitis acute	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Abscess jaw	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Cellulitis	0	2 (0.8)	0	0 (0, 0)	0.8 (-0.3, 1.9)
Peritonsillar abscess	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)
Pyelonephritis acute	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)
Sepsis	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)
Nervous system disorders (SOC)					
Stroke and TIA (FMQ)	2 (0.8)	1 (0.4)	1 (0.4)	0.4 (-1.0, 1.8)	-0.0 (-1.1, 1.1)
Cerebral infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Cerebrovascular accident	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Ischaemic stroke	1 (0.4)	0	1 (0.4)	0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Renal and urinary disorders (SOC)					
Renal & Urinary Tract Infection (FMQ)	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)
Pyelonephritis acute	0	0	1 (0.4)	-0.4 (-1.2, 0.4)	-0.4 (-1.2, 0.4)
Vascular disorders (SOC)					
Thrombosis (FMQ)	4 (1.6)	0	1 (0.4)	1.2 (-0.6, 3.0)	-0.4 (-1.2, 0.4)
Cerebral infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Deep vein thrombosis	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Pulmonary embolism	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Ischaemic stroke	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)

System Organ Class (SOC) FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	Thrombosis Arterial (FMQ)	3 (1.2)	0	1 (0.4)	0.8 (-0.8, 2.4)
Cerebral infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Myocardial infarction	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Ischaemic stroke	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Thrombosis Venous (FMQ)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Deep vein thrombosis	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Pulmonary embolism	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)

Source: adae.xpt; Software: R; MedDRA Version: 24.1

¹ Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2).

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is median 4 weeks (minimum 0.1, maximum 9.7 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; FMQ, EOT, end of treatment; FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class; TIA, transient ischemic attack; vs., versus

7.6.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation

AEs leading to permanent discontinuation of study treatment were uncommon in Part 1 of the study but reported in a slightly higher proportion of aprocitentan-treated patients (3% and 2%, respectively, for the 12.5 mg and 25 mg dose) as compared to placebo (1%; Table 29). In Part 2, AEs leading to treatment discontinuation were reported in 3.8% of subjects; the proportion was slightly higher among subjects who switched from the placebo arm (in Part 1) (5.1%) than among subjects who switched from the 12.5 mg arm (2.6%) or remained on the 25 mg dose (3.8%; Table 146). After review of the cases, AEs leading to discontinuation due to edema, elevated transaminases, and hypersensitivity appear to be related to aprocitentan. See Sections 7.6.5.1, 7.6.5.3, and 7.6.5.4 for further discussion of these events, respectively. AEs resulting in discontinuation that were adjudicated as MACE are discussed in Section 7.6.6 and narratives are provided in [Table 144](#).

Table 28. Subjects With Adverse Events¹ Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, PRECISION Study, Part 1

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)²	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)²
AE leading to permanent discontinuation	7 (2.9)	5 (2.0)	2 (0.8)	2.1 (-0.3, 4.4)	1.2 (-0.9, 3.3)
Cardiac disorders (SOC)					
Arrhythmia (FMQ) ³	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Ventricular extrasystoles	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
General disorders and administration site conditions (SOC)					
Face oedema	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Immune system disorders (SOC)					
Angioedema (FMQ) ³	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Allergic oedema	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Hypersensitivity (FMQ) ³	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Allergic oedema	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Infections and infestations (SOC)					
Viral Infection (FMQ) ³	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
COVID-19 pneumonia	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Bacterial Infection (FMQ) ³	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Root canal infection	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Investigations (SOC)					
Transaminases increased	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Metabolism and nutrition disorders (SOC)					
Hyperkalaemia	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Nervous system disorders (SOC)					
Stroke and TIA (FMQ) ³	1 (0.4)	1 (0.4)	1 (0.4)	-0.0 (-1.1, 1.1)	-0.0 (-1.1, 1.1)
Cerebrovascular accident (M)	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Ischaemic stroke (M)	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI) ²	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI) ²
	Renal and urinary disorders (SOC)	0	1 (0.4)	0	0 (0, 0)
Pollakiuria	0	1 (0.4)	0	0 (0, 0)	0.4 (-0.4, 1.2)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Pulmonary embolism	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Vascular disorders (SOC)					
Thrombosis (FMQ) ³	2 (0.8)	0	1 (0.4)	0.4 (-1.0, 1.8)	-0.4 (-1.2, 0.4)
Pulmonary embolism	1 (0.4)	0	0	0.4 (-0.4, 1.2)	0 (0, 0)
Ischaemic stroke (M)	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Hypotension (FMQ) ³	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Hypotension	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Thrombosis Arterial (FMQ) ³	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)
Ischaemic stroke (M)	1 (0.4)	0	1 (0.4)	-0.0 (-1.1, 1.1)	-0.4 (-1.2, 0.4)

Source: adae.xpt; Software: R; MedDRA Version: 24.1

¹ Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2).

² Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

³ Each FMQ is aligned to a single SOC based on clinical judgment. However, some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query and are not shown or counted in this table.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; FMQ, EOT, end of treatment; FDA medical query; M, MACE; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class; TIA, transient ischemic attack; vs., versus

7.6.5. Treatment-Emergent Adverse Events

TEAEs occurring at an incidence of $\geq 2\%$ in aprocitentan-treated subjects with a risk difference from placebo of $\geq 1\%$ during Part 1 are shown in [Table 29](#). Groupings of TEAEs occurring at an incidence of at least 2% of subjects in any aprocitentan arm during Part 1 are shown in [Table 30](#). As shown in [Table 30](#), AEs suggestive of fluid retention (Peripheral edema FMQ) and anemia (Anemia FMQ) were reported at a greater incidence in the aprocitentan arms as compared to the placebo arms. Additional analyses for edema/fluid retention and anemia are presented in [Section 7.6.5.1](#) and [Section 7.6.5.2](#), respectively.

Table 29. Treatment-Emergent Adverse Events¹ Occurring at ≥2% Incidence and ≥1% Greater Than Placebo, Safety Population, PRECISION Study, Part 1

Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference² (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference² (%) (95% CI)
Any AE	67 (27.6)	90 (36.7)	47 (19.4)	8.2 (0.6, 15.7)	17.3 (9.5, 25.1)
Oedema peripheral	16 (6.6)	35 (14.3)	5 (2.1)	4.5 (0.9, 8.1)	12.2 (7.5, 17.0)
Hemoglobin decreased	6 (2.5)	0	0	2.5 (0.5, 4.4)	0 (0, 0)
Face oedema	4 (1.6)	3 (1.2)	0	1.6 (0.0, 3.2)	1.2 (-0.2, 2.6)
Fluid retention	4 (1.6)	7 (2.9)	0	1.6 (0.0, 3.2)	2.9 (0.8, 4.9)
Dyspnea	1 (0.4)	4 (1.6)	1 (0.4)	-0.0 (-1.1, 1.1)	1.2 (-0.6, 3.0)
Headache	0	5 (2.0)	3 (1.2)	-1.2 (-2.6, 0.2)	0.8 (-1.5, 3.1)
Upper respiratory tract infection	0	6 (2.4)	4 (1.7)	-1.7 (-3.3, -0.0)	0.8 (-1.7, 3.3)

Source: adae.xpt; Software: R; MedDRA Version: 24.1

¹ Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2)

² Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; EOT, end of treatment; N, number of subjects in treatment arm; n, number of subjects with adverse event; vs., versus

Table 30. Adverse Events¹ by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, PRECISION Study, Part 1

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference² (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference² (%) (95% CI)
Blood and lymphatic system disorders (SOC)					
Anemia (FMQ)	9 (3.7)	3 (1.2)	0	3.7 (1.3, 6.1)	1.2 (-0.2, 2.6)
Haemoglobin decreased	6 (2.5)	0	0	2.5 (0.5, 4.4)	0 (0, 0)
Anaemia	1 (0.4)	2 (0.8)	0	0.4 (-0.4, 1.2)	0.8 (-0.3, 1.9)
General disorders and administration site conditions (SOC)					
Peripheral Edema (FMQ) ³	16 (6.6)	35 (14.3)	5 (2.1)	4.5 (0.9, 8.1)	12.2 (7.5, 17.0)
Oedema peripheral	16 (6.6)	35 (14.3)	5 (2.1)	4.5 (0.9, 8.1)	12.2 (7.5, 17.0)
Dizziness (FMQ) ³	2 (0.8)	5 (2.0)	1 (0.4)	0.4 (-1.0, 1.8)	1.6 (-0.3, 3.6)
Dizziness	2 (0.8)	2 (0.8)	1 (0.4)	0.4 (-1.0, 1.8)	0.4 (-1.0, 1.8)

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TRYVIO (aprocitentan)

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference² (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference² (%) (95% CI)
Infections and infestations (SOC)					
Viral Infection (FMQ) ³	7 (2.9)	3 (1.2)	3 (1.2)	1.6 (-0.9, 4.2)	-0.0 (-2.0, 1.9)
Respiratory tract infection viral	2 (0.8)	0	0	0.8 (-0.3, 2.0)	0 (0, 0)
Asymptomatic COVID-19	2 (0.8)	1 (0.4)	1 (0.4)	0.4 (-1.0, 1.8)	-0.0 (-1.1, 1.1)
COVID-19 pneumonia	2 (0.8)	1 (0.4)	1 (0.4)	0.4 (-1.0, 1.8)	-0.0 (-1.1, 1.1)
Nasopharyngitis (FMQ) ³	1 (0.4)	8 (3.3)	5 (2.1)	-1.7 (-3.6, 0.3)	1.2 (-1.7, 4.1)
Upper respiratory tract infection	0	6 (2.4)	4 (1.7)	-1.7 (-3.3, -0.0)	0.8 (-1.7, 3.3)
Nervous system disorders (SOC)					
Headache (FMQ) ³	0	5 (2.0)	3 (1.2)	-1.2 (-2.6, 0.2)	0.8 (-1.5, 3.1)
Headache	0	5 (2.0)	3 (1.2)	-1.2 (-2.6, 0.2)	0.8 (-1.5, 3.1)
Respiratory, thoracic and mediastinal disorders (SOC)					
Dyspnea (FMQ) ³	2 (0.8)	6 (2.4)	1 (0.4)	0.4 (-1.0, 1.8)	2.0 (-0.1, 4.1)
Dyspnoea exertional	1 (0.4)	2 (0.8)	0	0.4 (-0.4, 1.2)	0.8 (-0.3, 1.9)
Dyspnoea	1 (0.4)	4 (1.6)	1 (0.4)	-0.0 (-1.1, 1.1)	1.2 (-0.6, 3.0)

Source: adae.xpt; Software: R

¹ Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2).

Duration is 4 weeks.

² Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

³ Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC. Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class, vs., versus

7.6.5.1. Edema/Fluid Retention

Fluid retention is a known risk of ERAs. Preferred terms for edema-related AEs were pooled via grouped query and included fluid retention, oedema peripheral, face oedema, pulmonary oedema, and localised oedema. In Part 1 of the PRECISION study, an imbalance in edema (grouped query) was observed between the aprocitentan 12.5 mg and 25 mg arms (9% and 18%, respectively) and placebo arm (2%) ([Table 31](#)). There appeared to be a dose-response relationship. Time to onset was as early as the first week of treatment but continued throughout the study ([Figure 7](#)). In Part 2, edema AEs were reported in 17% of subjects ([Table 31](#)); the incidence was higher among subjects who switched from the placebo arm (23%) as compared to those subjects who switched from the 12.5 mg arm (16%) and those who remained on the 25 mg dose (12%; [Table 143](#)). SAEs of pulmonary edema were reported in one subject in the aprocitentan 25 mg arm in Part 1 and one subject in Part 2; narratives are provided below. Both SAEs of pulmonary edema were reported in the context of significantly elevated blood pressure that most likely precipitated the events.

Overall, the majority of edema events were reported as mild to moderate in severity, with six subjects discontinuing aprocitentan due to edema ([Table 31](#)). For information on changes in body weight, see Section [7.6.9.1](#). Subgroup analyses for Part 1 suggested a greater risk in subjects greater than 65 years old, in subjects taking amlodipine 10 mg as background therapy, and in subjects with lower levels of kidney function ([Table 142](#)).

Table 31. Analysis of Edema, by Grouped Query, Safety Population, PRECISION Study

	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N =242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Edema Adverse Events						
Edema (GQ)	22 (9.1)	44 (18.0)	5 (2.1)	121 (17.1)	8 (2.6)	4 (1.3)
Exposure (subject-years)	19	19	19	399	68	66
Severity						
Severe	0	3 (1.2)	0	2 (0.3)	1 (0.3)	0
Moderate	11 (4.5)	15 (6.1)	0	39 (5.5)	2 (0.6)	0
Mild	11 (4.5)	26 (10.6)	0	78 (11.1)	5 (1.6)	4 (1.3)
Serious	0	1 (0.4)	0	1 (0.1)	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	1 (0.4)	0	4 (0.6)	1 (0.3)	0
Resulting in hospitalization	0	1 (0.4)	0	1 (0.1)	0	0
Prior history of heart failure	5 (2.1)	12 (4.9)	2 (0.8)	15 (2.1)	1 (0.3)	0
No prior history of heart failure	17 (7.0)	32 (13.1)	3 (1.2)	106 (15.1)	7 (2.3)	4 (1.3)

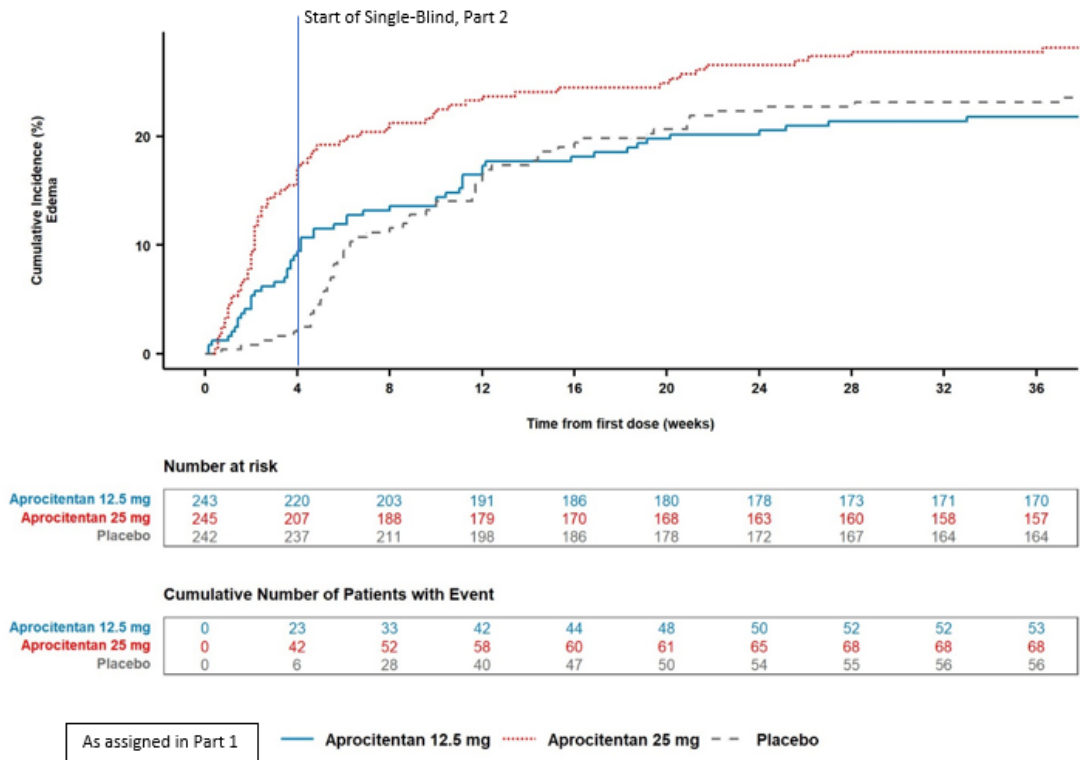
Source: adae.xpt; Software: R

Edema (GQ) contains fluid retention, hypervolemia, oedema peripheral, face oedema, pulmonary oedema, localised oedema.

Baseline weight for subjects in Part 2 was the weight reported at the end of Part 1. Baseline weight for subjects in Part 3 was the weight reported at the end of Part 2.

Abbreviations: DB, double-blind; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SB, single-blind

Figure 7. Time-to-Onset of Edema¹ (Grouped Query) Weeks 0 to 36², Safety Population, PRECISION Study, Parts 1 and 2



Source: adae.xpt; Software: R

¹ Edema GQ contains fluid retention, oedema peripheral, face oedema, pulmonary oedema, localized oedema. Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 1 up to the day before the start date of Part 2 (or EOT +30 days if the subject did not enter Part 2)

² Part 2 started at Week 4 and all subjects were assigned to aprocitentan 25 mg. From weeks 4-36, figure shows subjects as assigned in Part 1 to illustrate differences in treatment arms.

Abbreviations: AE, adverse event; EOT, end of treatment; GQ, grouped query

Edema SAEs

- Subject (b) (6) was a 67-year-old White male in the aprocitentan 25 mg arm who had a SAE of pulmonary edema, cardiac failure, and increased blood pressure on Study Day 8-12. The subject was admitted to the hospital with a diagnosis of heart failure with preserved ejection fraction with flash pulmonary edema after experiencing increasing dyspnea. Blood pressure upon arrival was 220/104 mmHg and chest X-ray showed early pulmonary edema. The subject's NT-proBNP value during hospitalization was not reported. The subject recovered after treatment (blood pressure upon hospital discharge was 123/65 mm/Hg) and the event was considered not related to the study drug. There was no action taken with study treatment. On Study Day 23, the subject presented to the emergency department with severe chest pain and peripheral edema that resolved after treatment with transdermal nitroglycerin and furosemide. There was no action taken with study treatment and the event was considered not related to the study drug. Prior to the study (at screening), the subject's individual background antihypertensive therapy included valsartan 300 mg and nifedipine 60 mg which were switched to SBAT per study protocol. Blood pressure at baseline was 150/82 mmHg.

- Subject (b) (6) was a 72-year-old Black male in the aprocitentan 25 mg arm who experienced an SAE of pulmonary edema, congestive heart failure, and hypertensive urgency on Study Day 134 to 137. The subject was admitted to the hospital with a diagnosis of congestive heart failure, pulmonary edema in the setting of hypertensive urgency, acute kidney injury on chronic kidney disease, and atrial flutter. Blood pressure upon arrival was reported as 209/60 mmHg and chest X-ray showed enlarged cardiac silhouette and pulmonary vasculature congestion. The subject's NT-proBNP value during hospitalization was not reported. The subject recovered after treatment with intravenous furosemide, nitrates, and hydralazine. Study treatment was interrupted due to the hypertension. The event was considered not related to study drug. Prior to the study (at screening), the subject's individual background antihypertensive therapy included SBAT and hydralazine (50 mg twice daily) which was discontinued at that time, per study protocol. The subject was restarted on study treatment on Study Day 147 and completed study Parts 2 and 3 in the aprocitentan 25 mg arm as scheduled.

Adjudicated MACE-Plus/Heart Failure Hospitalization

MACE-plus was defined as hospitalization for heart failure and adjudicated by the CAC. Over the course of the PRECISION study, eleven subjects experienced heart failure hospitalization adjudicated as MACE-plus, two of which were reported in Part 1 in the aprocitentan 25 mg arm ([Table 32](#)). One of the cases in Part 1 (SAE of pulmonary edema in Subject (b) (6)) is discussed in the prior section; the other event that was adjudicated as a heart failure hospitalization in Part 1 occurred in a subject who had chronic heart failure at baseline, which was reported as worsening. In Part 2, six subjects experienced events that were adjudicated as a heart failure hospitalization. Of these subjects, one had previously taken aprocitentan 25 mg during Part 1 and five had previously been assigned to placebo. Of those who were switched from placebo, three of the events occurred within the first 3 weeks of initiating aprocitentan. In Part 3, three subjects experienced events that were adjudicated as heart failure hospitalizations; 2 subjects in the aprocitentan 25 mg arm and 1 subject in the placebo arm ([Table 32](#)). Narratives for the adjudicated MACE-plus heart failure hospitalizations are provided in [Table 144](#). Heart failure events resulting in discontinuation were uncommon ([Table 32](#)).

Table 32. Adjudicated MACE-Plus, Safety Population, PRECISION Study

	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Heart Failure Adverse Events						
Exposure (patient-years)	19	19	19	399	68	66
Adjudicated MACE-plus (HF Hospitalization)	0	2 (0.8) ¹	0	6 ² (0.9)	2 (0.6)	1 (0.3) ³
Acute left ventricular failure	0	0	0	0	1 (0.3)	0
Cardiac failure	0	1 (0.4)	0	1 (0.1)	0	0
Cardiac failure acute	0	0	0	0	0	1 (0.3)
Cardiac failure chronic	0	1 (0.4)	0	1 (0.1)	0	0
Cardiac failure congestive	0	0	0	3 (0.4)	0	0
Dyspnea	0	0	0	0	1 (0.3)	0
Left ventricular failure	0	0	0	1 (0.1)	0	0
Resulting in discontinuation	0	0	0	3 (0.4)	0	0
Prior History of Heart Failure	0	1 (0.4)	0	2 (0.2)	1 (0.3)	0
No Prior History of Heart Failure	0	1 (0.4)	0	10 (1.4)	2 (0.6)	1 (0.3)

Source: adae.xpt; Software: JMP and R

¹ Includes Subject (b) (6) described above in the edema-related SAEs

² Five of the six subjects switched from placebo arm in Part 1

³ Subject AE occurred 3 weeks after rerandomization from aprocitentan 25 mg to placebo

Abbreviations: AE, adverse event; CI, confidence interval; DB, double-blind; HF, heart failure; MACE, major adverse cardiovascular event(s); N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SB, single-blind

7.6.5.2. Anemia

Anemia is a known risk of ERAs and is thought to be due in part to hemodilution. In Part 1 of PRECISION, AEs suggestive of anemia (FMQ narrow) were reported in the aprocitentan arms but not in the placebo arm; however, there was no evidence of a dose-response relationship (4% and 1% in the 12.5 mg and 25 mg dose groups, respectively; [Table 33](#)). In Part 2, anemia AEs were reported in 9% of aprocitentan-treated. In Part 3, the incidence was similar among treatment groups. All of the AEs were reported to be mild to moderate in severity, with the exception of two AEs. In Part 1, one subject (Subject (b) (6)) experienced severe anemia related to blood loss, and in Part 2, one subject (Subject (b) (6)) experienced severe and serious anemia, which was not associated with a bleeding event and resulted in a blood transfusion. Discontinuation of study treatment due to anemia was reported in one subject (Subject (b) (6)) in

Part 2 who experienced moderate “anemia of unknown etiology” and was treated with a blood transfusion. . Reported laboratory values for the two subjects with anemia not associated with a bleeding event show a decrease in hemoglobin of approximately 2-3 g/dL from their baseline. Narratives for these two subjects are provided below. Decreases in hemoglobin observed for the safety population are discussed further below.

Table 33. Analysis of Anemia, by FDA Medical Query (Narrow), Safety Population, PRECISION Study

	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Anemia Adverse Events						
Anemia (nFMQ)	9 (3.7)	3 (1.2)	0	63 (8.9)	6 (1.9)	4 (1.3)
Exposure (subject-years)	19	19	19	399	68	66
Severity						
Severe	1 (0.4)	0	0	1 (0.1)	0	0
Moderate	0	0	0	8 (1.1)	1 (0.3)	0
Mild	8 (3.3)	3 (1.2)	0	54 (7.7)	5 (1.6)	4 (1.3)
Serious	0	0	0	1 (0.1)	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	1 (0.1)	0	0
Resulting in hospitalization	0	0	0	1 (0.1)	0	0

Source: adae.xpt; Software: R

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; nFMQ, narrow FDA Medical Query; SB, single-blind

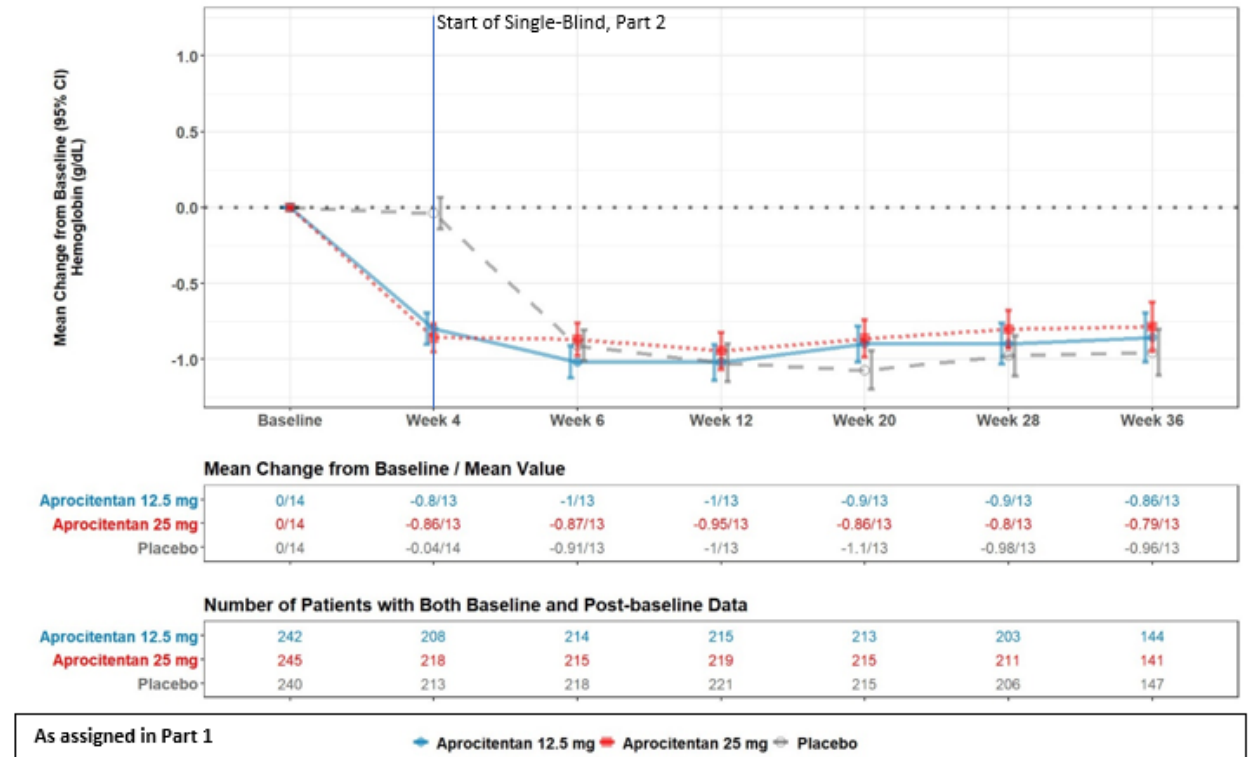
Anemia Narratives

- Serious AE
 - Subject (b) (6) was a 72-year-old White male in the aprocitentan 25 mg arm who experienced an SAE of anemia on Study Day 78 to 82. The subject presented to the emergency department with chest pain which was diagnosed as unstable angina pectoris, and a coronary artery bypass graft procedure was scheduled. On the same day, the subject was diagnosed with anemia (reported lab value: Hgb 8.6 g/dL). Fecal occult blood test was positive; however, no active bleeds were noted on endoscopy and colonoscopy. The event resolved after treatment with two units of red blood cells. No action was taken with study treatment and the event was considered not related to study treatment. Hemoglobin at baseline was 11.0 g/dL and reported as 9.1 g/dL and 9.2 g/dL, at the end of Parts 1 and 2, respectively. The last reported measurement was 9.9 g/dL, which was 2 months after the last dose of study drug.
- Resulted in Discontinuation
 - Subject (b) (6) was a 72-year-old White male in the aprocitentan 25 mg arm who received a blood transfusion for anemia of unknown etiology reported as a nonserious AE on Study Day 86-89. During screening on Day -69, it was reported that the subject experienced a nonserious event of anemia of unknown etiology of moderate intensity (reported value: Hgb 11.6 g/dL). During the study, the subject was treated with intramuscular cyanocobalamin from Study Day 42-57 (reported lab values: Hgb 8.8 g/dL, Day 42; Hgb 9.0 g/dL, Day 50; 8.7 g/dL, Day 67) and transfused with one unit of red blood cells on Study Day 86 (Hgb value not provided). Given the need for blood transfusion, the criterion for permanent study drug discontinuation was met and aprocitentan was discontinued on Day 89 (lab values not reported). Four days later on Day 93, hemoglobin was reported as 9.5 g/dL. The last reported hemoglobin was 12.1 g/dL on Day 121 at the safety follow-up visit.

Hemoglobin Decrease

Compared to the placebo group, the aprocitentan arms had a larger mean decrease from baseline in hemoglobin at Week 4 of treatment (mean decrease of 0.80 and 0.85 g/dL in aprocitentan 12.5 mg and 25 mg arms, respectively, compared to a decrease of 0.04 g/dL in the placebo arm) (Figure 8). In subjects reassigned from placebo to the aprocitentan 25 mg arm in Part 2, mean decreases from Week 4 baseline values were similar to values observed in subjects initially randomized to 12.5 mg and 25 mg at the start of the study; the mean decreases appeared to stabilize by Week 6 (Figure 8). In Part 3, mean hemoglobin levels rose in subjects rerandomized from aprocitentan to placebo, indicating that the effect on hemoglobin was reversible (Figure 9).

Figure 8. Mean Hemoglobin Change (g/dL) From Baseline to Week 36, Randomized Treatment Group , PRECISION Study, Part 1 and Part 2¹

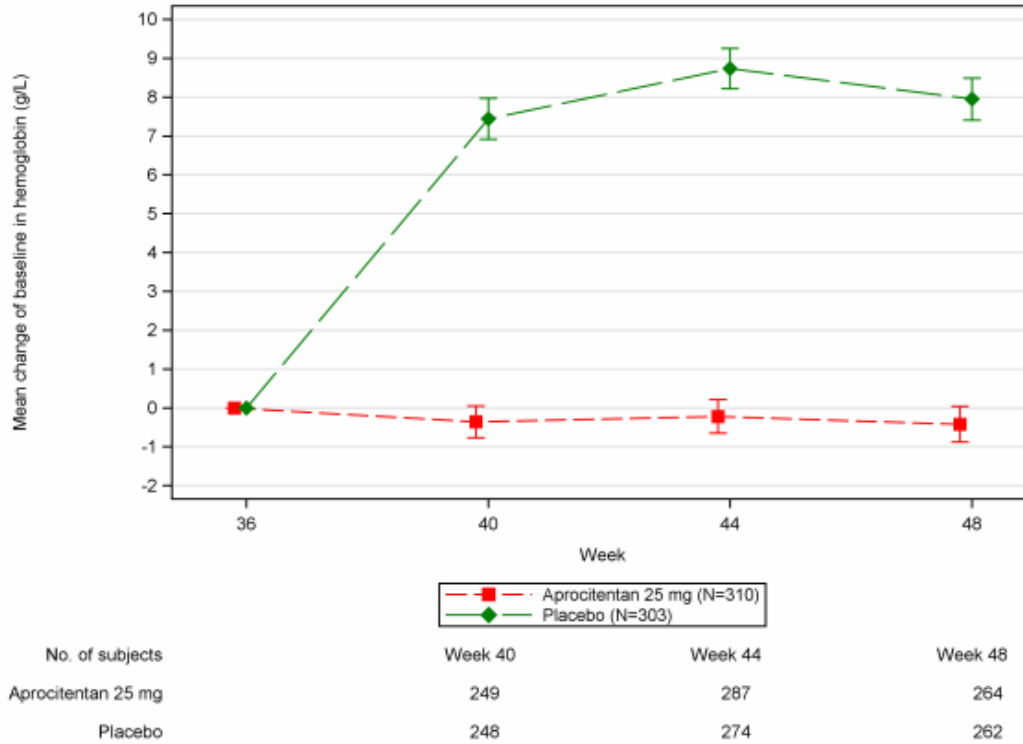


Source: adlb.xpt; Software: R

¹Part 2 started at Week 4 and subjects were assigned to aprocitentan 25 mg. From weeks 4-36, figure shows subjects as assigned in Part 1 to illustrate differences in treatment arms. Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.

Abbreviation: CI, confidence interval

Figure 9. Mean Hemoglobin Change (g/L) From Rerandomization (Week 36), by Visit, Safety Population, PRECISION Study, Part 3



Source: ID-080A301 CSR Final. Figure 15.3.4-1.3, verified by FDA reviewer; software: R
 Abbreviations: N, overall number of subjects; No., number of subjects in subset

Hemoglobin decreases exceeding specified levels are shown in [Table 145](#). In Part 1, the incidence of a hemoglobin decrease >2 g/dL compared to baseline was greater in subjects receiving aprocitentan (7% of 12.5 mg and 3% of 25 mg arms) compared to subjects treated with placebo (1%). A decrease in hemoglobin from baseline to below 10.0 g/dL in the initial 4-weeks was reported in 3% of subjects taking aprocitentan 12.5 mg, 2% of subjects taking aprocitentan 25 mg, versus 0 subjects taking placebo ([Table 145](#)).

7.6.5.3. Hepatotoxicity

Adverse Events

ERAs can cause hepatotoxicity (degree of risk varies among members of the class) and, as such, hepatotoxicity was an AESI for aprocitentan. During Part 1, no AEs suggestive of hepatic injury were reported in the aprocitentan arms ([Table 34](#)). During Part 2, 6 (0.9%) subjects reported AEs within the Hepatic injury and Hepatic failure narrow FMQ; of these, Hepatitis B was reported for one subject and Hepatitis C was reported for one subject. All of these events were reported to be mild to moderate in severity. In Part 3, AEs with this narrow FMQ were reported in 2.3% of subjects who were rerandomized to placebo arm as compared to <1% of subjects randomized to remain in the aprocitentan arm.

Table 34. Analysis of Hepatic Injury and Hepatic Failure, by FDA Medical Query (Narrow), Safety Population, PRECISION Study

	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Hepatic Injury and Hepatic Failure Adverse Events						
Hepatic Injury and Hepatic Failure (nFMQs)	0	0	2 (0.8)	6 (0.9)	1 (0.3)	7 (2.3)
ALT increased	0	0	1 (0.4)	3 (0.4)	1 (0.3)	5 (1.7)
AST increased	0	0	1 (0.4)	2 (0.3)	1 (0.3)	3 (1.0)
Hepatic function abnormal	0	0	0	1 (0.1)	0	1 (0.3)
Hepatitis B	0	0	0	1 (0.1)	0	0
Hepatitis C	0	0	0	1 (0.1)	0	0
Liver injury	0	0	1 (0.4)	1 (0.1)	0	0
Exposure (subject-years)	19	19	19	399	68	66
Severity						
Severe	0	0	0	0	0	0
Moderate	0	0	0	4 (0.6)	0	0
Mild	0	0	2 (0.8)	2 (0.3)	1 (0.3)	7 (2.3)
Serious	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
Resulting in discontinuation	0	0	0	1 (0.1)	0	1 (0.3)
Resulting in hospitalization	0	0	0	0	0	0

Source: adae.xpt; Software: R

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; nFMQ, narrow FDA Medical Query; SB, single-blind

Liver-Related Laboratory Parameters

[Table 35](#) provides the incidence of hepatic laboratory parameter elevations at any postbaseline visit by treatment arm. Elevations in ALT or AST $\geq 3x$ ULN were not reported at a higher incidence in the aprocitentan as compared to placebo arms during Part 1. During Part 2, elevations in ALT or AST $\geq 3x$ ULN were reported in 1% and 0.7% of subjects, respectively.

Table 35. Incidence of Hepatic Safety Laboratory Parameter Elevations at Any Postbaseline Visit by Treatment Arm, Safety Population, PRECISION Study

Laboratory Abnormality	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
ALT						
$\geq 1X$ ULN	37/224 (16.5)	40/223 (17.9)	41/217 (18.9)	186/699 (26.6)	52/309 (16.8)	66/300 (22.0)
$\geq 3X$ ULN	0/224 (0)	1/223 (0.4)	2/217 (0.9)	7/699 (1.0)	5/309 (1.6)	3/300 (1.0)
$\geq 5X$ ULN	0/224 (0)	0/223 (0)	1/217 (0.5)	3/699 (0.4)	2/309 (0.6)	1/300 (0.3)
$\geq 10X$ ULN	0/224 (0)	0/223 (0)	1/217 (0.5)	1/699 (0.1)	0/309 (0)	0/300 (0)
$\geq 20X$ ULN	0/224 (0)	0/223 (0)	0/217 (0)	0/699 (0)	0/309 (0)	0/300 (0)
AST						
$\geq 1X$ ULN	11/226 (4.9)	24/223 (10.8)	29/216 (13.4)	122/700 (17.4)	42/309 (13.6)	38/300 (12.7)
$\geq 3X$ ULN	0/226 (0)	1/223 (0.4)	2/216 (0.9)	5/700 (0.7)	4/309 (1.3)	3/300 (1.0)
$\geq 5X$ ULN	0/226 (0)	0/223 (0)	1/216 (0.5)	1/700 (0.1)	0/309 (0)	2/300 (0.7)
$\geq 10X$ ULN	0/226 (0)	0/223 (0)	1/216 (0.5)	0/700 (0)	0/309 (0)	1/300 (0.3)
$\geq 20X$ ULN	0/226 (0)	0/223 (0)	0/216 (0)	0/700 (0)	0/309 (0)	0/300 (0)
ALP						
$\geq 2X$ ULN	0/223 (0)	0/223 (0)	0/216 (0)	3/700 (0.4)	0/309 (0)	0/300 (0)
$\geq 3X$ ULN	0/223 (0)	0/223 (0)	0/216 (0)	0/700 (0)	0/309 (0)	0/300 (0)
Total bilirubin						
$\geq 2X$ ULN	0/223 (0)	2/222 (0.9)	0/216 (0)	2/700 (0.3)	0/309 (0)	2/300 (0.7)
$\geq 5X$ ULN	0/223 (0)	0/222 (0)	0/216 (0)	0/700 (0)	0/309 (0)	0/300 (0)
$\geq 8X$ ULN	0/223 (0)	0/222 (0)	0/216 (0)	0/700 (0)	0/309 (0)	0/300 (0)
Direct bilirubin						
$\geq 2X$ ULN	0/207 (0)	0/212 (0)	2/209 (1.0)	1/699 (0.1)	0/309 (0)	1/300 (0.3)
$\geq 5X$ ULN	0/207 (0)	0/212 (0)	0/209 (0)	0/699 (0)	0/309 (0)	0/300 (0)

Source: adlb.xpt; Software: R

The frequency represented here are based on peak levels.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DB, double-blind; N, number of subjects in group; n, number of subjects meeting criteria; SB, single-blind; ULN, upper limit of normal

Case Level Analysis

To further evaluate the risk of hepatotoxicity, subject level data from the PRECISION study and an additional Phase 2 study (Study 201) were reviewed by DHN. Per the DHN review:

- Based on hepatocellular scatterplots (eDISH), there was no imbalance in liver analytes nor cases concerning for significant liver injury in Study 201.
- Based on hepatocellular scatterplots (eDISH), there was no imbalance in liver analytes during the 4-week double-blinded placebo-controlled period (Part 1) in Study 301.
- DILI adjudication of high interest cases in the PRECISION study identified four cases in Part 2 (aprocitentan 25 mg arm), which included two highly likely cases (based on positive rechallenge), and two possible cases ([Table 36](#)).

Table 36. List of Subjects With Highly Likely or Possible Causality Scores for Drug-Induced Serious Hepatotoxicity, Safety Population, PRECISION Study

ID	Causality Score*	Alternate diagnosis	Study	Age (yr)	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)^	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)**
(b) (6)	2	NA	ID-080A301	36	F	White	No	No	139	[8]	220	80	104	0.29	6.5
	2	NA	ID-080A301	63	F	White	No	No	205	[4]	284	210	366	0.7	2.4
	4	Unknown	ID-080A301	32	F	White	No	No	107	1	119	60	104	0.82	3.5
	4	Hepatitis B	ID-080A301	54	M	Asian	No	No	84	[59]	454	158	104	0.53	13.4
								<i>Max</i>	205	1	454	210	366	0.82	13.4
								<i>Min</i>	84	[59]	119	60	104	0.29	2.4

NA = not applicable

R-value = (ALT/ULN) + (AP/ULN); R > 5: hepatocellular; R between 2 & 5 mixed; R < 2 cholestatic

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULN (104) was imputed if AP never rose to > ULN

** ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

^[] day values means the drug continued for that many days after injury onset. Thus, the *minimum* latency after drug stop is the highest bracketed number.

Source: Table 5, DHN Consult Review; DILI Team

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; da, study day; DHN, Division of Hepatology and Nutrition; DILI, drug-induced liver injury; ID, identifier; max, maximum; min, minimum; NA, not applicable; yr, year

According to the DHN review, the mean latency period for the highly likely and possible DILI events after initiation of aprocitentan was 134 days (approximately 4 months; range 84-205 days). Of note, DILI with a long latency period has been observed with other ERAs (bosentan, macitentan, ambrisentan). In general, the elevations in liver enzymes resolved/improved with discontinuation of aprocitentan. As previously mentioned, in two cases, elevations reoccurred with aprocitentan rechallenge; these two highly likely cases of DILI are further described below.

- Subject (b) (6): The subject was a 63-year-old white female in the aprocitentan 25 mg arm who experienced elevated liver enzymes on Study Day 206; ALT was reported as 284 U/L (8.4 x ULN) and AST was reported as 210 U/L (6.2 x ULN). The subject's baseline medication history included levothyroxine (0.125 mg daily), atorvastatin (20 mg daily). Her atorvastatin dose was increased to 40 mg daily on Study Day 189 (17 days prior to the event). Treatment for the elevated enzymes included stopping atorvastatin on Day 209 and interrupting aprocitentan from Study Days 210 to 222. The event resolved without sequelae on Day 223. On Study Day 312 (61 days after rechallenge), the subject again experienced mild elevation of transaminases, AST was 136 U/L (4 x ULN) and ALT was 84 U/L (2.5 x

ULN) with no symptoms reported; AP rose as well but remained < ULN. Total bilirubin (TB) remained normal throughout. ALT and AST climbed a bit further and the aprocitentan was permanently discontinued on Study Day 316.

At baseline, her enzymes were normal [ALT was 26 U/L, AST was 24 U/L, and TB was 3µmol/L (SI units)]. She started the study in the aprocitentan 12.5 mg arm, and her ALT and AST remained within normal levels for the 4 weeks, reported as 24 U/L and 20 U/L at the end of Part 1. The subject started aprocitentan 25 mg on Day 28 and her liver enzymes were reported as normal until Study Day 206 (178 days later). She had no associated symptoms. Ultrasound showed steatosis, but no obvious etiology for acute liver injury. No other liver evaluation tests (autoimmune markers, viral tests) were available. Alcohol history was not provided. [Figure 10](#) below provides the liver analytes by Study Day. Return to baseline had not yet occurred at the last follow-up.

Figure 10. Liver Enzyme and Total Bilirubin Levels, by x ULN and Study Day, Subject (b) (6), Safety Population, PRECISION Study



Source: Figure 6, DHN Consult Review; DILI Team
 Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DHN, Division of Hepatology and Nutrition; DILI, drug-induced liver injury; RI, run-in; SBAT, standard background antihypertensive; SCR, screening; ULN, upper limit of normal; x, times

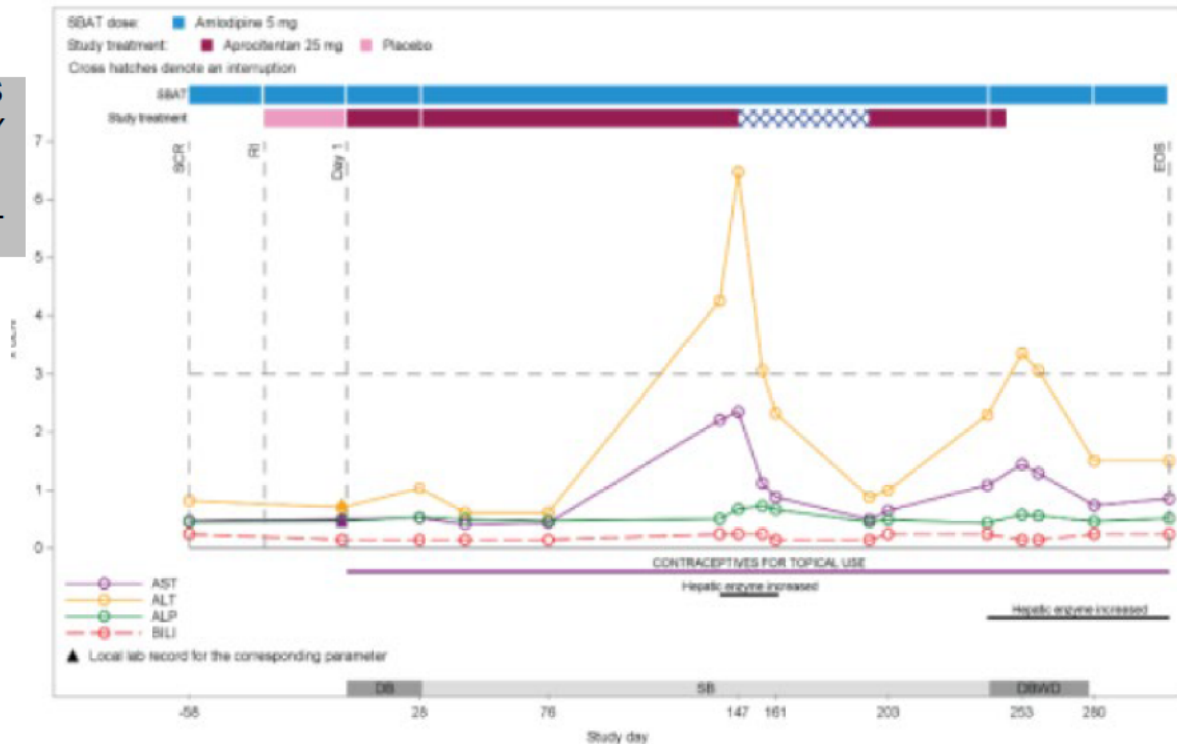
DHN Assessment

This case is assessed as highly likely due to aprocitentan treatment based on the positive rechallenge which strongly suggests a causal relationship with aprocitentan and not the atorvastatin. The statin was not restarted. The latencies from aprocitentan start, dose increase and rechallenge were 208, 179 and 61 days, respectively. The shorter latency on rechallenge would be consistent with DILI. Both rises in aminotransferases declined to normal or near normal with holding aprocitentan. We note that evaluation testing was limited, and so recurrent infection or

passage of gallstones could compete. Her sex and obesity increase her risk of gallstones. However, she was asymptomatic, and ultrasound did not report gallstones. The Applicant suggests the first enzyme peak was due to the statin and the second due to steatosis found on ultrasound. We do not agree. The more logical explanation is a positive aprocitentan rechallenge. Her BMI was 40 kg/m² at baseline, and there was no mention of marked weight gain followed by weight loss with the second peak. The steatosis is likely chronic and irrelevant to the acute injury.

- Subject (b) (6): The subject was a 36-year-old white female in the aprocitentan 25 mg arm who experienced elevated liver enzymes on Study Day 139; ALT, AST, AP, and TB were 145 U/L (4.3 x ULN), 75 U/L, 54 U/L and 0.29 mg/dL, respectively. CK was normal. No symptoms were mentioned. The study drug continued without change. On Study Day 147, ALT and AST peaked at 220 U/L (6.5 x ULN) and 80 U/L, respectively. Still no symptoms were mentioned. The study drug was held on Study Day 148. The liver enzymes fell to normal or nearly normal by Day 196. On the same day, aprocitentan 25 mg was restarted. On Study Day 240 (44 days after rechallenging), ALT and AST were 78 and 37 U/L, respectively. AP and TB remained < ULN throughout both aminotransferase elevations. Aprocitentan was permanently discontinued on Day 247 due to the aminotransferase elevations. ALT and AST rose to second peak of 114 (3.3 x ULN) and 49 U/L on Study Day 253. Thereafter, ALT improved with >50% decline from second peak occurring within 27 days, and AST was back to normal ([Figure 11](#)). At baseline, the subject's BMI was 28 kg/m². Relevant medical history included just the targeted disease. Alcohol history was not provided. Concurrent medications relative to DILI risk were nil. The subject's ALT, AST, AP, and TB were 24 U/L, 17 U/L, 50 U/L and 0.2 mg/dL, respectively, at baseline. ALT return to baseline had not yet occurred at last follow-up. Evaluation testing was not done.

Figure 11. Liver Enzyme and Total Bilirubin Levels, by xULN and Study Day, Subject (b) (6) Safety Population, PRECISION Study



Source: Figure 7, DHN Consult Review; DILI Team

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DHN, Division of Hepatology and Nutrition; DILI, drug-induced liver injury; RI, run-in; SBAT, standard background antihypertensive therapy; SCR, screening; ULN, upper limit of normal

DHN Assessment

This case was assessed as highly likely DILI due to aprocitentan because the positive rechallenge strongly suggested a causal relationship. The latencies from aprocitentan start and from rechallenge were 140 and 44 days, respectively. The shorter latency on rechallenge would be consistent with DILI. Both rises in aminotransferases declined to normal or near normal with holding aprocitentan. Evaluation testing was limited, and so recurrent infection or passage of gallstones could compete. However, she was asymptomatic. The Applicant noted there was an “absence of apparent confounding factors” and that attribution to aprocitentan could not be “ruled out.” There were no obvious competing etiologies.

7.6.5.4. Hypersensitivity Reactions

During Part 1, hypersensitivity-related AEs were reported in 0.8% of subjects taking aprocitentan 12.5 mg and 0.4% of subjects taking 25 mg compared with none reported for placebo. During Part 2, one subject (Subject (b) (6)) taking 25 mg had an SAE of allergic dermatitis requiring hospitalization. The narrative is provided below.

Subject (b) (6) was a 73-year-old female randomized to placebo during Part 1. On Study Day 31 (2 days after starting aprocitentan 25 mg in Part 2), the subject experienced a nonserious AE of allergic dermatitis on her face, trunk, both arms and legs. Her symptoms intensified and she

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was hospitalized with a diagnosis of allergic dermatitis on Day 39 to 43. Study treatment was interrupted on Study Days 40 to 43 and restarted on Day 44. Two days later, on Day 46, the allergic dermatitis (reported as nonserious) recurred (positive rechallenge) and the study medication was permanently discontinued on the same day. The event resolved on Day 50 and was assessed as related to aprocitentan.

7.6.6. MACE

MACE was defined as cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke, and events were adjudicated by the CAC ([Table 37](#)). MACE events would be expected in this population and given the design of the study, data are challenging to interpret. On face, they do not raise concern. A discussion of the adjudicated MACE deaths is provided in Section [7.6.2](#). Narratives for subjects with adjudicated MACE are provided in [Table 144](#).

Table 37. Adjudicated¹ MACE by Category, Safety Population, PRECISION Study

MACE Category ² Preferred Term	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB-WD)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Any AE adjudicated as MACE	3 (1.2)	1 (0.4)	1 (0.4)	8 (1.1)	2 (0.6)	2 (0.7)
Cardiovascular death	0	0	0	5 (0.7)	0	0
CVA	0	0	0	2 (0.3)	0	0
Death	0	0	0	1 (0.1)	0	0
Subdural haemorrhage	0	0	0	1 (0.1)	0	0
Sudden cardiac death	0	0	0	1 (0.1)	0	0
Nonfatal MI	1 (0.4)	0	0	3 (0.4)	2 (0.6)	0
Acute MI	0	0	0	1 (0.1)	0	0
Angina unstable	0	0	0	0	1 (0.3)	0
Myocardial infarction	1 (0.4)	0	0	2 (0.3)	1 (0.3)	0
Nonfatal stroke	2 (0.8)	1 (0.4)	1 (0.4)	0	0	2 (0.7)
Cerebral infarction	1 (0.4)	0	0	0	0	0
CVA	0	1 (0.4)	0	0	0	0
Haemorrhage intracranial	0	0	0	0	0	1 (0.3)
Ischemic stroke	1 (0.4)	0	1 (0.4)	0	0	1 (0.3)
Severity ³						
Severe	3 (1.2)	1 (0.4)	1 (0.4)	6 (0.9)	2 (0.6)	2 (0.7)
Moderate	0	1 (0.4)	0	1 (0.1)	0	0
Mild	0	0	0	1 (0.1)	0	0
Serious	3 (1.2)	1 (0.4)	1 (0.4)	8 (1.1)	2 (0.6)	1 (0.3)
Resulting in discontinuation	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.3)	1 (0.3)	2 (0.7)
Resulting in hospitalization	2 (0.8)	1 (0.4)	1 (0.4)	5 (0.7)	2 (0.6)	2 (0.7)

Source: adae.xpt; Software: R

¹ An independent Central Adjudication Committee was responsible for adjudicating, in a standardized and blinded fashion, all AEs and SAEs identified by the Investigator or Sponsor which indicated potential MACE.

² MACE were defined as: cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke.

³ Severity is determined by investigator.

Abbreviations: AE, adverse event; CVA, cerebrovascular accident; DB, double-blind; DB-WD, double-blind withdrawal; MACE, major adverse cardiac event; MI, myocardial infarction; N, overall number of subjects in treatment arm; n, number of subjects meeting criteria; SAE, serious adverse event; SB, single-blind

7.6.7. Pregnancies During the PRECISION Study

One subject ((b) (6)) discontinued study treatment due to pregnancy during Part 2 of the PRECISION study. Estimated exposure to aprocitentan 25 mg was 7 weeks of the first trimester. A normal baby was born at 38 weeks' gestation. The narrative is provided below:

- Subject (b) (6): A 34-year-old White female informed the study site that she tested positive on a urine pregnancy test on Study Day 139 ((b) (6)). The study medication (aprocitentan 25 mg) and background therapy were permanently discontinued on the same day. The pregnancy was confirmed by the site (B-hCG was 1157 mIU/mL on Study Day 141). Her previous B-hCG test was negative on Study Day 90 (49 days prior). The Investigator explained to her the potential complications which might affect the fetus/baby. She decided to continue with the pregnancy and was referred to a gynecologist. Three weeks later, the subject visited the ED for increased BP, reported as 180/90 mmHg, and was started on labetalol 100mg twice daily. All obstetrical ultrasounds of the fetus/fetal anatomy were normal, blood tests, genetic tests (Myriad panel and Alpha-Fetoprotein Test) were normal; the estimated delivery date was (b) (6). She completed her Safety Follow-Up visit on Study Day 189 with a normal visit and labs reported. At 38-weeks' gestation, the subject was admitted for labor induction and endorsed good fetal movement. Cesarean section was performed due to failure to progress in labor and a male infant was born with weight 8 lbs 13.1 oz. There were no delivery complications, no neonatal illness, no need for resuscitation, no need for Intensive Care Unit admission, and no congenital anomalies were diagnosed. The subject was discharged from the hospital with routine postpartum follow-up. Baseline characteristics for the subject included obesity (BMI 35.2 kg/m²) and a normal eGFR (119 mL/min/1.73m²). Obstetrical history included five previous pregnancies complicated by pre-eclampsia; one spontaneous abortion followed by four live births delivered at 39 weeks and all healthy babies. Concomitant medications included ferrous fumarate, escitalopram 10 mg, and use of three methods of contraception (nonoxynol gel as needed, ethinyl estradiol/norethisterone acetate tablets daily, and condom usage as needed).

7.6.8. Laboratory Findings

Laboratory findings associated with AESIs are described in Section 7.6.5. Analyses of other biochemistry data did not reveal findings of concern. A summary of the findings for kidney function is provided below. Overall, a small decrease in eGFR from baseline was observed in subjects taking aprocitentan, with the greatest decrease occurring during the initial 6 weeks of treatment in subjects randomized to aprocitentan 25 mg.

7.6.8.1. Kidney Function

Kidney function analyte values exceeding specified levels for Part 1 are provided in [Table 39](#). The risk difference versus placebo for a $\geq 25\%$ decrease in eGFR was higher in the patients treated with aprocitentan 25 mg (3.1%) compared to those treated with 12.5 mg (0.4%). One subject (Subject (b) (6)) in the aprocitentan 25 mg arm experienced an eGFR decrease of $\geq 50\%$ compared with none in the other treatment arms. However, the subject was no longer

taking the study treatment at the time of laboratory collection (at Week 4 end of Part 1 Visit), due to hospitalization for heart failure, with the last dose of study medication approximately 2 weeks prior. The subject's eGFR at baseline was 38 ml/min/1.73 m². The narrative for this hospitalization is provided in (MACE-plus) [Table 144](#).

Table 38. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, PRECISION, Part 1

Laboratory Parameter	Aprocitentan	Aprocitentan	Placebo N=242 n/N _w (%)	Aprocitentan 12.5 mg vs Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs Placebo Risk Difference (%) (95% CI)
	12.5 mg N=243 n/N _w (%)	25 mg N=245 n/N _w (%)			
Creatinine, high (mg/dL)					
Level 1 (≥1.5X baseline)	1/224 (0.4)	3/224 (1.3)	0/219 (0)	0.4 (-0.4, 1.3)	1.3 (-0.2, 2.8)
Level 2 (≥2X baseline)	0/224 (0)	0/224 (0)	0/219 (0)	0 (0, 0)	0 (0, 0)
Level 3 (≥3X baseline)	0/224 (0)	0/224 (0)	0/219 (0)	0 (0, 0)	0 (0, 0)
eGFR, low (ml/min/1.73 m ²)					
Level 1 (≥25% decrease)	6/225 (2.7)	12/223 (5.4)	5/219 (2.3)	0.4 (-2.5, 3.3)	3.1 (-0.5, 6.7)
Level 2 (≥50% decrease)	0/225 (0)	1/223 (0.4)	0/219 (0)	0 (0, 0)	0.4 (-0.4, 1.3)
Level 3 (≥75% decrease)	0/225 (0)	0/223 (0)	0/219 (0)	0 (0, 0)	0 (0, 0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.

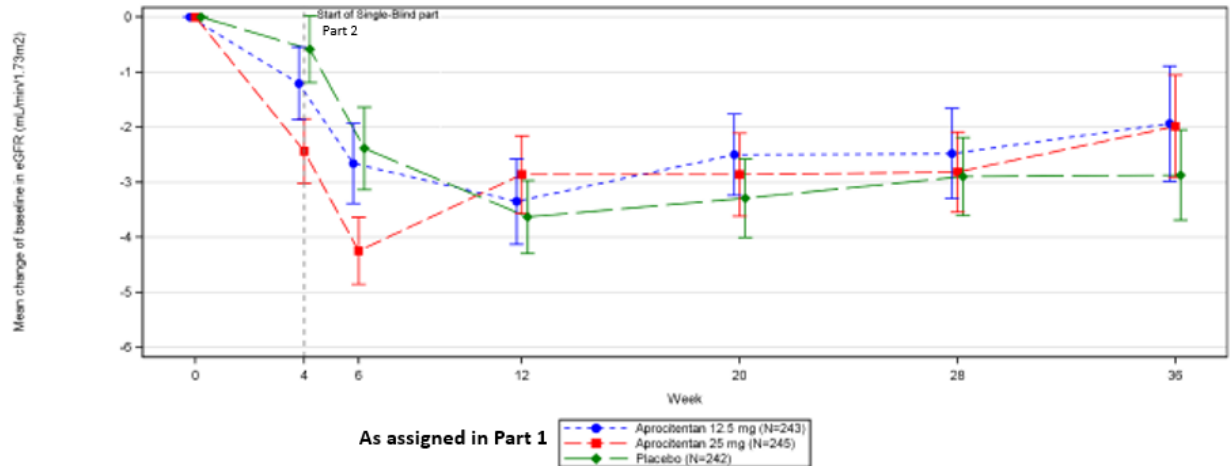
Duration is median 4 weeks (minimum 0.1, maximum 9.7 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Mean changes in eGFR from baseline up to Week 36 are provided in [Figure 12](#). The initial decrease in eGFR appeared to be greater in patients randomized to aprocitentan 25 mg (-2.4 mL/min/1.73 m²) as compared to those randomized to aprocitentan 12.5 mg arm (-1.2 mL/min/1.73 m²) and placebo (-0.6 mL/min/1.73 m²) ([Figure 12](#)). After approximately 6 weeks, no further decrease in mean eGFR was observed in the aprocitentan 25 mg arm.

Figure 12. Mean Change in Estimated Glomerular Filtration Rate (mL/min/1.73 m²) From Baseline to Week 36¹, Randomized Treatment Group, PRECISION Study, Part 1 and Part 2



No. of subjects	Week 4	Week 6	Week 12	Week 20	Week 28	Week 36
Aprocitentan 12.5 mg	223	212	214	209	198	145
Aprocitentan 25 mg	229	215	219	213	212	136
Placebo	219	214	218	216	199	149

Source: ID-080A301 CSR Final. Figure 15.3.4-1.3, verified by FDA reviewer; software: R
¹Part 2 started at Week 4 and all subjects were assigned to aprocitentan 25 mg. From weeks 4-36, figure shows subjects as assigned in Part 1 to illustrate differences in treatment arms.
 Abbreviations: eGFR, estimated glomerular filtration rate; N, overall number of subjects; no., number of subjects in subgroup

In Part 1 of the study, AEs of acute kidney injury were reported in one subject randomized to 12.5 mg aprocitentan and two subjects randomized to 25 mg aprocitentan as compared to no subjects randomized to placebo. The events were reported to be mild to moderate in severity and no action was taken with study treatment in these subjects. In Part 2, four subjects (0.6%) experienced an AE of acute kidney injury. One of these subjects (Subject (b) (6)) experienced a SAE. Two other subjects (Subject (b) (6) and Subject (b) (6)) discontinued treatment for the event. Review of the narratives suggested other factors likely contributed to these events. The narrative for the SAE is provided below. The narrative for Subject (b) (6) is provided in (Mace-Plus) [Table 144](#).

Acute Kidney Injury Narrative

- Serious AE

Subject (b) (6) was a 65-year-old White male in the aprocitentan 25 mg arm who had a SAE of gastroenteritis and acute kidney injury due to severe dehydration on Study days 80 to 91. The subject was admitted to the hospital with a diagnosis of acute kidney injury after experiencing diarrhea and vomiting. The subject’s creatinine clearance was reported as 2.3 (no unit) upon admission. Study treatment was interrupted on Day 80 and the events resolved with treatment on Day 84. The event was considered not related to the study drug, which was restarted on Day 91. The subject had an eGFR of 34 ml/min/1.73m² at baseline, and at the start of Part 2 (Day 37), an eGFR of 41 ml/min/1.73m².

7.6.9. Vital Signs

Other than weight gain, analyses of vital signs data did not reveal any safety concerns. Body weight changes in Part 1 and information on QT interval (QT) prolongation are provided below.

7.6.9.1. Weight Gain

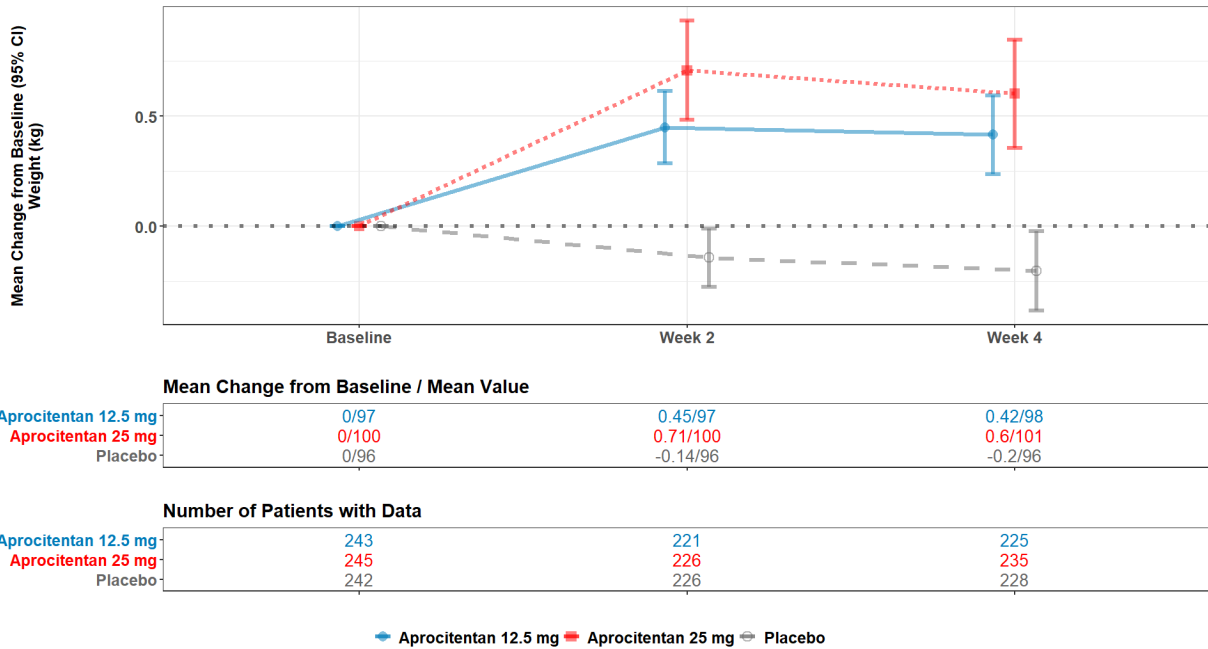
In Part 1 and 2, five subjects had nonserious “weight increased” AEs, all in the aprocitentan 25 mg arm. One event was graded as moderate in severity and the remaining graded as mild.

During Part 1, the mean weight change from baseline for the aprocitentan treated arms was 0.4 kg and 0.6 kg respectively and -0.2 kg for the placebo arm ([Figure 13](#)). Clinically significant weight gain (i.e., >5 kg) from baseline was seen in 0.8%, 3.3%, and 0% of subjects randomized to aprocitentan 12.5 mg, 25 mg, and placebo, respectively, in Part 1 (

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Table 39). These increases are likely due to fluid retention, a known effect of ERAs.

Figure 13. Mean Weight Change from Baseline Over Time, Safety Population, PRECISION Study, Part 1



Source: advs.xpt; Software: R
 Vertical bars show 95% confidence intervals.
 Abbreviation: CI, confidence interval

Table 39. Body Weight, Safety Population, PRECISION

	Study Part 1 (4-Week DB)			Study Part 2 (32-Week SB)	Study Part 3 (12-Week DB)	
	Aprocitentan 12.5 mg N=243 n (%)	Aprocitentan 25 mg N=245 n (%)	Placebo N=242 n (%)	Aprocitentan 25 mg N=704 n (%)	Aprocitentan 25 mg N=310 n (%)	Placebo N=303 n (%)
Parameter: Body Weight (kg)						
Mean Change from Baseline (SD)	0.4 (1.4)	0.6 (1.8)	-0.2 (1.2)	-0.1 (2.8)	-0.3 (2.2)	-0.7 (2.1)
Min, Max	-10.3, 6.0	-8.3, 10.9	-4.1, 4.8	-19.9, 18.5	-23.6, 17.6	-13.0, 9.8
Increased >2 kg from baseline ¹	29 (11.9)	49 (20.0)	8 (3.3)	206 (29.3)	49 (15.8)	33 (10.9)
Increased >5 kg from baseline ¹	2 (0.8)	8 (3.3)	0 (0)	41 (5.8)	6 (1.9)	6 (2.0)

Source: advs.xpt; Software: R

¹ At any visit during treatment. Baseline weight for subjects in Part 2 was the weight reported at the end of Part 1. Baseline weight for subjects in Part 3 was the weight reported at the end of Part 2.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; SB, single-blind

7.6.9.2. Assessment for Potential QT Prolongation

The potential risk for QT prolongation and Torsade de Pointe with aprocitentan was evaluated in a thorough QT study (ID-080-108) which was reviewed by the Interdisciplinary Review Team for Cardiac Safety Studies. The thorough QT study was a prospective, single-center, randomized, double-blind, placebo- and moxifloxacin- controlled, 4-way crossover Phase 1 study to assess the effect of multiple therapeutic and suprathreshold doses of aprocitentan on the corrected QT interval duration in healthy subjects. The suprathreshold dose (100 mg), which is 8 times the therapeutic dose (12.5 mg), provided approximately 3-fold high clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis. The results of the study show that at 8 times the maximum recommended dose, clinically significant corrected QT interval prolongation was not observed. Further details can be found in the Interdisciplinary Review Team Review dated August 14, 2023.

7.7. Key Safety Review Issues

7.7.1. Hepatotoxicity

Issue

The PRECISION study data suggests aprocitentan can cause elevations of transaminases without hyperbilirubinemia.

Background

Hepatotoxicity, including liver failure, has been reported with ERAs and is described in the FDA-approved labeling for these products. Macitentan, the parent compound of aprocitentan, includes hepatotoxicity as a warning and precaution in the labeling and recommends a baseline measurement of liver analytes (including total bilirubin) and repeat measurements as clinically indicated. Two products in the ERA class, bosentan and sparsentan, have a REMS for hepatotoxicity.

Assessment

There was no imbalance in findings for liver analytes between aprocitentan and placebo exposure in the PRECISION study or Study 201, although, the randomized periods for comparison were relatively short at four to eight weeks and latencies for other ERA hepatotoxicity have been several months. There were no cases of jaundice in PRECISION and hence no Hy's Law or cholestatic jaundice cases across all study periods. The characterization of the risk is limited due to the size of the study population.

Case level analysis of the PRECISION study safety data by DHN suggests that aprocitentan can cause hepatotoxicity. In Part 2, there were two subjects with liver enzyme elevations of greater than 5-fold the upper limit of normal which were assessed as highly likely related to the use of aprocitentan. Both subjects had positive rechallenges. One subject had potential hepatocellular injury (i.e., predominantly aminotransferase elevation) while the other had a mixed injury (i.e.,

both aminotransferase and alkaline phosphatase elevation). The enzyme elevations were modest without hyperbilirubinemia and were resolved or nearly resolved at the last follow-up visit after aprocitentan discontinuation.

Conclusion

Although data indicate potential risk, the findings in the development program as well as the findings with macitentan suggest that risk can be adequately mitigated with labeling, which will include a warning and precaution for hepatotoxicity. Labeling will include a recommendation for monitoring of liver analytes, to be checked prior to initiation and periodically during treatment. Aprocitentan will not be recommended for use in patients with decompensated cirrhosis or acute liver disease. Postmarketing surveillance will include enhanced pharmacovigilance for a period of 5 years with required submission of all serious cases of liver injury as 15-day alert reports and summary analyses provided in the periodic safety reports.

7.7.2. Embryo-Fetal Toxicity

Issue

Nonclinical data with macitentan suggest an adverse effect of aprocitentan on the developing fetus when administered to a pregnant woman. In EFD studies with aprocitentan, while no embryo-fetal toxicity, including teratogenic effects, were observed at 5-fold and 29-fold the human exposure at MRHD in rats and rabbits, respectively, the highest dose of aprocitentan tested in the rat EFD study was too low to fully characterize reproductive risk. There are uncertainties about the embryo-fetal toxicity risk of ERAs in humans. Data regarding pregnancy outcomes in first trimester exposure of ERAs are limited.

Background

Female adults of reproductive potential (FRP; ages 18-49 years) are included in the target population for aprocitentan and represented 5% of the PRECISION study population. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the general U.S. population, the estimated background risk of major birth defects is 2-4% and risk of miscarriage is 15-20%. Hypertension during pregnancy is considered to be high-risk. Prescribers of antihypertensives commonly use inhibitors of the renin-angiotensin system, particularly angiotensin-converting enzyme inhibitors and ARBs, in the treatment of hypertension in FRP. These products have a boxed warning for fetal toxicity when used in the second and third trimester and should be discontinued as soon as possible when pregnancy is detected. Valsartan (ARB) was used as background therapy in the PRECISION study.

Assessment

The PRECISION study excluded pregnant subjects and required monthly pregnancy tests and contraception use. There was one unplanned pregnancy reported during Part 2 of PRECISION (Study Day 139). The subject had taken aprocitentan 25 mg daily for approximately 6 weeks (first trimester exposure) prior to discontinuation due to the pregnancy. The outcome was reported as a normal baby born at 38 weeks gestation (see Section [7.6.6](#) for details).

Aprocitentan is not proposed as first-line therapy which may limit its use and minimize the risk in FRP. In addition, all ERA products are approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of embryo-fetal toxicity. The Division of Cardiology and Nephrology and the Division of Risk Management agree that a REMS with ETASU is also necessary for aprocitentan. However, the REMS for aprocitentan will differ from the REMS for other ERA products (approved for PAH or IgA nephropathy). The elements agreed upon by these FDA Divisions for the REMS for aprocitentan consist of ETASU A and B, an implementation system, and a timetable for submission of assessments. Prescriber certification and specialized training (ETASU A) on the risk of embryo-fetal toxicity helps ensure all prescribers are educated on the risk. Specialized training is expected to improve identification of at-risk patients and encourage healthcare providers to counsel patients about the risk and the actions to take to prevent fetal exposure and minimize exposure during pregnancy. Pharmacy certification (ETASU B) helps ensure only certified pharmacies are dispensing aprocitentan after verifying that prescribers of aprocitentan are certified. The REMS for aprocitentan is structured to ease healthcare burden while supporting the safe use of aprocitentan. For a detailed description, see the REMS review by Cristen Lambert, PharmD.

In addition to the REMS, the risk will be included in labeling as a Boxed Warning and approval will include a postmarketing requirement for a descriptive study of pregnancy outcomes.

Conclusion

The risk of embryo-fetal toxicity with aprocitentan can be mitigated with the use of effective contraception in FRP. A REMS with ETASU is required to ensure the benefits outweigh the risk; the ETASU is necessary to ensure prescribers are aware of the risk and the need to counsel patients on the use of contraception and regular pregnancy testing to prevent and minimize fetal exposure to aprocitentan. Pharmacy certification is necessary to confirm that the prescriber is certified in the REMS prior to dispensing of aprocitentan to patients. Further, the risk will be communicated in labeling and an observational pregnancy safety study will be required to assist in further characterizing the risk.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

A 50 mg dose of aprocitentan was studied in subjects with severe renal impairment and compared to age-, sex-, body weight-, and height-matched subjects with normal renal function in Study AC-080-105. The maximum plasma concentration (C_{max}) was similar between groups, with a geometric mean ratio of 1.04 (90% CI 0.85-1.28). The time to maximum concentration (T_{max}) increased from 5 hours in healthy controls to 7.6 hours in subjects with severe renal impairment. A lower clearance led to a longer half-life in those with severe renal impairment, increasing from 47.4 hours in healthy subjects to 53.2 hours in those with severe renal impairment. The AUC_{0-t} and $AUC_{0-\infty}$ were 32% and 34% higher, respectively, in those with severe renal impairment compared to healthy subjects. Please see Section [14.2](#) for a full

discussion of results. No dose adjustment is required in patients with mild to severe renal impairment. Because the effect of kidney failure or dialysis on aprocitentan pharmacokinetics has not been studied, use of aprocitentan in these patients is not recommended.

Hepatic Impairment

A 25 mg dose of aprocitentan was studied in subjects with moderate hepatic impairment and compared to age-, sex-, body weight-, and height-matched subjects with normal hepatic function in Study ID-080-109. The $C_{\max}$ was similar between groups, with a geometric mean ratio of 1.03 (90% CI 0.86-1.24). The $T_{\max}$ was 4 hours for healthy controls and those with moderate hepatic impairment. The mean half-life increased from 48.3 hours in healthy subjects to 56.4 hours in those with moderate hepatic impairment. The AUC_{0-t} and $AUC_{0-\infty}$ were 22% and 23% higher, respectively, in those with moderate hepatic impairment compared to healthy subjects. Please see Section [14.2](#) for a full discussion of results. Based on the results, no dose adjustment is required in patients with mild or moderate hepatic impairment. Because the effect of severe hepatic impairment on aprocitentan pharmacokinetics has not been studied, use of aprocitentan in these patients is not recommended.

Age

Elderly subjects (inclusion criteria: 65-80 years, inclusive) generally had higher $C_{\max}$ and AUC_{τ} values in Study AC-080-101. After multiple doses, the $C_{\max}$ and AUC_{τ} ratio of geometric means were 1.31 and 1.21 for elderly compared to nonelderly subjects (inclusion criteria: 18 to 45 years, inclusive), respectively. Please see Section [14.2](#) for a full discussion of results. No dose adjustment is recommended for elderly subjects taking aprocitentan.

Race

A 25 mg dose of aprocitentan was studied in healthy Japanese and Caucasian subjects in Study ID-080-107. Overall, after multiple doses, the $C_{\max}$ and AUC_{τ} ratio of geometric means were 1.02 and 1.08 for Japanese subjects compared to Caucasian subjects, respectively. Please see Section [14.2](#) for a full discussion of results. No dose adjustment is recommended based on race for aprocitentan.

Sex

Females generally had higher plasma concentrations compared to males in Study AC-080-101. After a single dose, the $C_{\max}$ and $AUC_{0-\infty}$ ratio of geometric means were 1.25 and 1.27 for females compared to males, respectively. After multiple doses, the $C_{\max}$ and AUC_{τ} ratio of geometric means were 1.38 and 1.37, respectively, for females compared to males. Please see Section [14.2](#) for a full discussion of results. No dose adjustment is recommended for females taking aprocitentan.

8.2. Extrinsic Factors

Drug Interactions

Metabolic Pathway

Based on the mass balance study (Study AC-080-104), two metabolic pathways contribute to $\geq 25\%$ of aprocitentan elimination – glucosidation of aprocitentan to metabolite M3 by UGT1A1 and UGT2B7 (accounts for approximately 25% of the administered dose), and hydrolysis of aprocitentan to metabolite M1 which then undergoes several other reactions leading to metabolites A1, A4, A5, M4, M5, M6, M11, and M13 (accounts for approximately 31.5% of the administered dose).

While M1 accounts for 31.5% of the administered dose, based on results from in vitro studies, it is believed that M1 is formed by both chemical and enzymatic hydrolysis. Incubation of radiolabeled aprocitentan with human liver microsomes led formation of M1 (4.3% of total chromatogram radioactivity); however, M1 was also observed in experiments without microsomes or a nicotinamide adenine dinucleotide phosphate-regenerating system (present at 9.3% and 6.4% total chromatogram radioactivity, respectively, in comparable conditions). When incubated with hepatocytes, M1-M6 was generated, but no metabolite contributed to more than 5% of total chromatogram radioactivity. M1 was also seen in the control experiment without liver cells and accounted for 8.7% of total chromatogram radioactivity.

For a complete discussion of aprocitentan metabolism, please see in vitro studies in Section [14.1](#) and the mass-balance study in Section [14.2](#).

Effect of Other Drugs on Aprocitentan

As glucosidation of aprocitentan to metabolite M3 accounts for approximately 25.2% of the administered dose, uridine diphosphate-glucuronosyltransferase (UGT) inducers may lead to a decrease in aprocitentan concentration and efficacy; however, no clinical drug-drug interaction studies were conducted with aprocitentan and UGT inducers.

Effect of Aprocitentan on Other Drugs

The effect of 25 mg aprocitentan at steady state was evaluated on a single dose of 10 mg rosuvastatin, a breast cancer resistance protein substrate, in healthy male subjects. Aprocitentan increased the $C_{\max}$ of rosuvastatin by 40%. The AUC_{0-t} and $AUC_{0-\infty}$ were minimally affected (geometric mean ratios of 1.07 and 0.99, respectively). The mean half-life of rosuvastatin decreased from 17.9 hours to 14.1 hours, though this change was not statistically significant ($p=0.14$).

The effect of a 50 mg aprocitentan dose at steady state concentrations was evaluated on a single dose of 8 mg midazolam, a cytochrome P450 3A4 substrate, in healthy male subjects. Aprocitentan did not have an effect on the $C_{\max}$ of midazolam (ratio of geometric means 1.04, 90% CI 0.88-1.23); however, the $C_{\max}$ of 1-hydroxy midazolam was decreased (ratio of geometric means 0.86, 90% CI 0.7-1.1). The mean half-life for midazolam was unchanged when administered with aprocitentan; however, the mean half-life of 1-hydroxy midazolam increased

to a mean of 7.7 hours when administered with aprocitentan compared to 5.8 hours when midazolam was administered alone. The AUC_{0-t} and $AUC_{0-\infty}$ of midazolam were minimally increased when administered with aprocitentan (both ratios of geometric means were 1.14). The AUC_{0-t} and $AUC_{0-\infty}$ of 1-hydroxy midazolam were minimally decreased when administered with aprocitentan (geometric mean ratios of 0.95 and 0.98, respectively).

Dosing Recommendations

No dose adjustments related to drug interactions are proposed. UGT inducers may decrease aprocitentan concentrations and thus may lower the efficacy of aprocitentan, though the extent to which aprocitentan concentration and efficacy may decrease has not been studied. UGT inducers may not produce any clinically meaningful effect on aprocitentan concentration, as only 25.2% of the dose is metabolized through glucosidation, and multiple UGT enzymes are involved in aprocitentan glucosidation. If aprocitentan is an ineffective treatment in patients on UGT inducers, these patients will likely be treated as other nonresponders, and discontinuation is likely. Therefore, labeling language for those on UGT inducers is not necessary.

Food Effect

In Study AC-080-101, effects of food on plasma PK variables were assessed after a single 100 mg dose of aprocitentan. Exposure increased with food, with the geometric mean ratios (fed/fasted) of 1.73 and 1.23 for C_{max} and $AUC_{t-\infty}$, respectively. The T_{max} decreased from 9 to 5 hours when fed, though the range was similar (4 to 10 hours for fasted, and 5 to 12 hours for fed). The labeling states that aprocitentan can be taken with or without food. The labeling is in line with the Phase 3 study where subjects were to take aprocitentan each morning, irrespective of food intake.

8.3. Plans for Pediatric Drug Development

The investigational product triggers the Pediatric Research Equity Act as a new active ingredient for the proposed indication. The Applicant submitted their agreed upon Agreed Initial Pediatric Study Plan requesting a full waiver of pediatric assessments because “a favorable therapeutic benefit/risk profile is not expected,” other “safe and efficacious therapeutic classes of antihypertensive drugs can be used,” aprocitentan does not represent a meaningful therapeutic benefit over existing therapies, and because of the potential for teratogenicity.

Based on the available data, the Division and Pediatric Review Committee agree that a full waiver of pediatric studies should be granted because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients with hypertension. Given the product’s safety profile, aprocitentan will not be approved as initial (first-line) therapy for the treatment of hypertension in adults. While the development program demonstrated that the product is effective in lowering blood pressure in adults, the size of the effect was modest (LS mean difference between aprocitentan and placebo of ~4 mmHg). Given these issues, the benefit-risk profile is expected to be unfavorable for pediatric patients with hypertension.

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

Embryo-fetal toxicities in rats and rabbits, the results of male and female fertility studies in rats, and potential reproductive organ toxicities are discussed in Section 7.1. Nonclinical data supporting labeling language are shown in the table below by labeling section.

Table 40. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	<i>Animal data</i> In pregnant rats, oral administration of macitentan at doses of 3, 10 and 150 mg/kg/day throughout organogenesis, resulted in fetal abnormalities, which included defects in the cardiovascular and mandibular arch fusion malformations, at all the doses tested. The aprocitentan exposure at the lowest dose tested (3 mg/kg/day) was approximately equivalent to the clinical exposure at the MRHD based on AUC. In pregnant rabbits, oral administration of macitentan at doses of 2.5, 12.5 and 25 mg/kg/day throughout organogenesis, resulted in fetal abnormalities, which included defects in the cardiovascular and mandibular arch fusion malformation, at all the doses tested. The aprocitentan exposure at the lowest dose tested (2.5 mg/kg/day) was approximately 15-fold the clinical exposure at the MRHD based on AUC. In the pre- and postnatal developmental (PPND) study in rats, oral administration of macitentan at doses of 10, 50 or 250 mg/kg/day during pregnancy and the lactational period resulted in reduced pup survival and impairment of the male fertility of the offspring at all doses. The aprocitentan exposure at the lowest dose tested (10 mg/kg/day) was approximately 2-fold the clinical exposure at the MRHD based on AUC.
8.2 Lactation	In rats, aprocitentan, which is an active metabolite of macitentan, was consistently observed in milk samples across all time points after oral administration of ¹⁴C-labeled macitentan.
8.3 Females and Males of Reproductive Potential	Other ERAs have shown an adverse effect on spermatogenesis in humans and/or animals. Aprocitentan may impair fertility in males of reproductive potential. It is not known whether the effects on fertility would be reversible.
13.1 Impairment of Fertility	In a fertility and early embryonic development (FEED) study in female rats, oral administration of aprocitentan prior to mating at doses of 10, 50, or 250 mg/kg/day resulted in minimally-increased pre-implantation loss at ≥ 50 mg/kg/day, which is approximately 23-fold the clinical exposure at the MRHD based on AUC at 250 mg/kg/day. No impact on fertility was observed at 10 mg/kg/day, which represents 5-fold the clinical exposure at the MRHD based on AUC. In male rats, oral administration of aprocitentan for 15 weeks had no effect on fertility or spermatogenesis at doses up to 250 mg/kg, which is approximately 52-fold the clinical exposure at the MRHD based on AUC. In repeat dose toxicity studies, oral administration of aprocitentan resulted in testicular tubular degeneration/atrophy in male rats and dogs at the high dose of 250 mg/kg/day and at doses ≥ 25 mg/kg/day, respectively, which is approximately 41- and 53-fold the AUC at the MRHD, respectively. The testicular toxicity was not evident in male rats and dogs at 50 mg/kg/day and 5 mg/kg/day, respectively, which

Labeling Section	Nonclinical Data
	represents approximately 14- and 11-fold the clinical exposure at the MRHD based on AUC.

Source: Pharmacology/toxicology reviewer-generated table.

Abbreviations: AUC, area under the curve; ¹⁴C, carbon 14 isotope radiolabel; ERA, endothelin receptor antagonist; FEED, fertility and early embryonic development; MRHD, maximum recommended high dose, PPND, postnatal developmental

9. Product Quality

The Office of Pharmaceutical Quality review team has assessed NDA 217686 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

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

The Applicant has adequately disclosed financial arrangements with clinical investigators and the PRECISION study appears to have been conducted in compliance with U.S. regulations pertaining to Good Clinical Practice. No clinical sites were inspected. The primary efficacy findings were assessed after a randomized, double-blind treatment period and were based on objective and standardized measurements. None of the PRECISION study sites enrolled a large number of study subjects or drove the primary efficacy findings and review of the data did not raise other serious concerns that would warrant a clinical site inspection (e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles).

11. Advisory Committee Summary

The application provides substantial evidence of the product's effectiveness in lowering blood pressure. Given the safety profile of aprocitentan, the product will not be approved as initial (first-line) therapy for the treatment of hypertension in adults. Given the intended use as well as the measures that could be put in place to mitigate risk, the application was not felt to raise significant or controversial issues that would merit outside expertise or public discussion. As such, no Advisory Committee Meeting was held for this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

ACT-132577, later called aprocitentan, was developed by Actelion Pharmaceuticals, Ltd. (Actelion) for the treatment of resistant hypertension under IND 122772. The IND was opened on October 17, 2014, with a single-center, three-part, phase 1 study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACT-132577 in healthy male and female subjects. The study was deemed safe to proceed on November 20, 2014.

On June 19, 2017, sponsorship of the IND was transferred from Actelion to Idorsia Pharmaceuticals Ltd. (Idorsia) who continued developing aprocitentan for the treatment of hypertension, to lower blood pressure, in adult subjects who are not adequately controlled on three antihypertensive drugs from different classes, including a diuretic. Idorsia did not develop aprocitentan as a first-line monotherapy but rather as a background of other antihypertensives.

Aprocitentan's clinical development program mainly consisted of 10 clinical pharmacology studies and 2 studies in subjects with hypertension:

- Study AC-080A201: A phase 2, double-blind, placebo-controlled, dose-finding study investigating the blood pressure reduction effect of aprocitentan as monotherapy in naïve or antihypertensive subjects
- Study 080A301: A multi-center, blinded, randomized, parallel-group, phase 3 study with aprocitentan in subjects with resistant hypertension (PRECISION)

The Division of Cardiology and Nephrology (DCN) provided feedback on several aspects of product development via advice letters dated August 17, 2015, January 12, 2018, November 23, 2018, April 29, 2019, July 17, 2019, November 13, 2019, June 15, 2020, November 4, 2020, and December 02, 2021. Additional information on milestone meetings and key events may be found in the below table.

NDA 217686
TRYVIO (aprocitentan)

Table 41. Summary of Key Regulatory History, PRECISION Study

Topic	Key Regulatory History
Milestone meetings and key events	<u>Jul 28, 2014</u> : Pre-IND meeting
	<u>Oct 17, 2014</u> : IND-opening study submitted
	<u>Jun 19, 2017</u> : Change of ownership from Actelion Pharmaceuticals Ltd. to Idorsia Pharmaceuticals Ltd.
	<u>Sep 15, 2017</u> : End-of-phase 2 meeting
	<u>Sep 22, 2022</u> : PRECISION Study Topline results meeting
	<u>Mar 3, 2022</u> : Pre-NDA meeting planned (cancelled by Idorsia after receiving DCN's meeting preliminary comments)
	<u>Jun 2, 2022</u> : Type C REMS meeting
	<u>Nov 28, 2022</u> : Pre-NDA meeting planned (cancelled by Idorsia after receiving DCN's meeting preliminary comments)
	<u>Dec 19, 2022</u> : Idorsia submitted an NDA under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Source: DARRTS

Abbreviations: DCN, FDA Division of Cardiology and Nephrology; IND, investigational new drug, Ltd., limited; NDA, new drug application; DARRTS: FDA's Document Archiving, Reporting and Regulatory Tracking System

On December 19, 2022, pursuant to Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, Idorsia submitted a marketing application for aprocitentan relying on the results of PRECISION. The review classification was Standard, and the user fee goal date was December 19, 2023.

Along with the original NDA submission, Idorsia submitted the proposed proprietary name TRYVIO. This name was considered conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA). A Grant Letter was issued on March 16, 2023.

After consultation with the REMS Oversight Committee (ROC), the Division of Risk Management (DRM) and DCN concluded that the [REDACTED] ^{(b) (4)} REMS proposed by Idorsia was not adequate to mitigate the risk of embryo-fetal toxicity associated with aprocitentan. It was determined that a REMS with Elements to Assure Safe Use (ETASU) was necessary to mitigate this risk. On August 8, 2023, the Agency shared this decision with Idorsia asking them to submit a revised REMS to the NDA file. On September 6, 2023, Idorsia submitted the revised REMS. The September 6, 2023, submission constituted a major amendment to the application. The user fee goal date was extended by three months; making the new goal date March 19, 2024.

Of note, in the agreed iPSP dated March 16, 2018, Idorsia requested a full waiver of the requirement to submit pediatric assessments for aprocitentan because a favorable therapeutic benefit/risk profile is not expected in the pediatric population. Specifically, given that aprocitentan was developed as a 4th-line add-on therapy in patients with difficult-to-control hypertension and due to the safety concerns of Endothelin Receptor Antagonists (ERAs), the use of aprocitentan was not justified in any age group of the pediatric population with hypertension. The application was discussed with the Pediatric Review Committee (PeRC) on January 9, 2024. The PeRC agreed with granting a full waiver on the basis that TRYVIO fails to represent a

meaningful therapeutic benefit over existing therapies and is unlikely to be used in the pediatric population.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

Evaluation of pharmacological activity of aprocitentan on endothelin (ET) receptors are summarized in the table below. In *in vitro* studies using Chinese hamster ovary (CHO) cells expressing human ET_A or ET_B receptors, aprocitentan showed antagonistic properties at both ET receptor subtypes (ET_A and ET_B) in a competitive radioligand binding assay and inhibited the ET-1-induced increase in cytosolic Ca²⁺ in a functional assay. In the isolated rat aorta and trachea, aprocitentan inhibited ET-1 (ET_A-mediated) and sarafotoxin S6c (ET_B-mediated) induced contractions, respectively. In the *in vivo* study, aprocitentan dose-dependently increased ET-1 concentrations at doses ≥ 3 mg/kg in normotensive rats, suggesting that aprocitentan blocked the binding of ET-1 to ET_B receptors in normal rats.

Table 42. Aprocitentan Receptor Subtype Selectivity and Functions

Study	Findings
Antagonist potency in CHO cells expressing human ET _A and ET _B receptors.	Aprocitentan inhibited binding of ¹²⁵ I-ET-1 to ET _A and ET _B receptors with IC ₅₀ values of 3.4±0.4nM (n=4) and 987±185nM (n=4), respectively.
Inhibition of intracellular calcium in CHO-K1 cells expressing recombinant human ET _A or ET _B receptors.	Aprocitentan inhibited the ET-1-induced increase in cytosolic Ca ²⁺ with a geometric mean K _b value of 5.5nM on ET _A (n=5) and 319nM on ET _B (n=4).
Inhibition of ET-1-induced contraction in isolated rat aorta (denuded endothelium) and trachea (denuded epithelium).	ET _A -mediated contraction: aprocitentan inhibited the ET-1-induced contraction in rat aorta (pA ₂ value 6.7±0.2) ET _B -mediated contraction: aprocitentan inhibited the sarafotoxin S6c-mediated contraction in rat trachea (pA ₂ value 5.5±0.3)
Effect of aprocitentan (0.3, 1, 3, 10, 30, 100, and 300 mg/kg, oral gavage, single) on ET-1 plasma concentrations in normotensive male Wistar rats.	Aprocitentan dose-dependently increased ET-1 concentrations at doses ≥ 3 mg/kg (starting at plasma concentration of 1.53±0.04 pg/mL) compared to vehicle in normotensive Wistar rats, suggesting that aprocitentan blocked the binding of ET-1 to ET _B receptors in normal rats.

Source: Pharmacology/toxicology reviewer generated table based on Study Reports B-07.246, B-12.108, B-05.057. and B-14.017
Abbreviations: CHO, Chinese hamster ovary; ET, endothelin; Ca²⁺, calcium, IC₅₀, half maximal inhibitory concentration; K_b, equilibrium dissociation constant of a ligand determined by means of a functional assay; ¹²⁵I iodine-125 radioisotope; pA₂, negative logarithm of the molar concentration of antagonist that causes a 2-fold shift to the right of an agonist concentration-response curve

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Proof-of-concept for the efficacy of aprocitentan was assessed in in vivo animal models. As summarized in the table below, various hypertension rat models were used to evaluate potential effects of aprocitentan on hemodynamic parameters.

Aprocitentan showed acute antihypertensive effects, including decreased mean arterial pressure (MAP), in salt-sensitive and volume-dependent hypertensive (i.e., deoxycorticosterone acetate [DOCA]-salt rat and Dahl-S rat) or spontaneously hypertensive (SHR) rat models. The long-term effect of aprocitentan on hemodynamics and potential for end organ damage was further assessed in DOCA-salt rats. Results showed that aprocitentan improved renal blood flow and renal vascular resistance, in addition to decreased MAP, and a tendency for improved left ventricular weight, aorta and coronary artery thickness, and N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma concentration.

Table 43. Pharmacodynamic Efficacy of Aprocitentan in Animal Models of Hypertension

Study	Findings
Study No.: B-14.016 Study title: Effect of ACT-132577 on blood pressure and heart rate in conscious hypertensive rats. Species/strain: DOCA-salt rat (established with combination of unilateral nephrectomy, implantation of pellets of the mineralocorticoid analog DOCA and supply of 1% sodium chloride in drinking water), Dahl-S rat (genetic salt-sensitive model with a supply of 1% sodium chloride in drinking water), and SHR. Number/sex/group: 6/male/group Dose: DOCA-salt and Dahl-S rats: 0, 0.3, 1, 3, 10, 30, 100, and 300 mg/kg SHR: 0, 1, 3, 10, 30, 100, and 300 mg/kg Route and dosing frequency: Oral gavage/single. Method: Hemodynamic parameters were measured via radiotelemetry implanted devices.	<i>DOCA-salt rat</i> Dose-dependent decrease mean arterial pressure (MAP) in conscious rats without affecting heart rate (HR). Maximum decrease in blood pressure (BP) was 41±7 mmHg at 300 mg/kg and the ED₅₀≥3 mg/kg. <i>Dahl-S rat</i> Dose-dependent decrease MAP in conscious rats without affecting HR. Maximum decrease in BP was 35±6 mmHg at 100 mg/kg and the ED₅₀≥3 mg/kg. <i>SHR</i> Dose-dependent decrease MAP in conscious rats without affecting HR. Maximum decrease in BP was 18±4 mmHg at 100 mg/kg and the ED₅₀≥3 mg/kg.
Study No.: B-16.033 Study title: Chronic Effects of ACT-132577 in DOCA-salt Hypertensive Rats Species/strain: Rat/Wistar (DOCA-salt). Number/sex/group: 6 (Set I) and 8-10 (Set II)/male/group. Dose: Aprocitentan 1, 10 and 100 mg/kg/day Route and dosing frequency: Oral gavage/ daily for 4 weeks. Method: Hemodynamic parameters were measured via radiotelemetry implanted devices.	Aprocitentan dose-dependently decreased MAP (2, 19 and 21 mmHg decrease at 1, 10 and 100 mg/kg/day, respectively) and improved renal blood flow and renal vascular resistance. Aprocitentan tended to improve body weight gain, left ventricular weight, aorta, and heart coronary artery thickness, as well as NT-proBNP plasma concentrations (control: 31.4±3 pg/mL, DOCA-vehicle: 336±128 pg/mL, ACT-132577 1 mg: 282±72 pg/mL, 10 mg: 202±31 pg/mL, 100 mg: 193±32 pg/mL). Aprocitentan did not ameliorate relative right kidney weight, kidney histopathological changes (hydronephrosis, tubulonephrosis, interstitial nephritis and glomerular changes), heart weights and cardiomyopathy (interstitial fibrosis with inflammatory cell infiltration and a minimal to moderate coronary thickening (tunica media and intima)) when compared to control DOCA-salt treatment rats. No effect on water intake and urine volume was observed.

Source: Pharmacology/toxicology reviewer generated table based on Study Reports B-14.016 and B-16.033.

Abbreviations: BP, blood pressure; Dahl-S, Dahl-sensitive (rats); DOCA, deoxycorticosterone acetate; ED₅₀, effective dose for half of specimens tested; HR, heart rate; MAP, mean arterial pressure; NT-proBNP; N-terminal pro-brain natriuretic peptide; SHR, spontaneously hypertensive rat

Aprocitentan was studied in combination with other antihypertensive drugs (an angiotensin II receptor blocker, valsartan; an angiotensin converting enzyme inhibitor, enalapril; and a calcium channel blocker, amlodipine) in DOCA-salt and SHR rats to evaluate the additive/synergistic effects, as shown in the table below.

Table 44. Pharmacodynamic Efficacy of Aprocitentan With Other Antihypertensive Drugs

Study	Findings
Study no.: B-15.067 Study title: Effect of aprocitentan or Spironolactone or in Combination with Valsartan on Blood Pressure and Heart Rate in Conscious DOCA-Salt Rats Species/strain: Rat/Wistar (DOCA salt) Number/sex/group: 6-10/male/group Dose: aprocitentan 10 mg/kg, spironolactone 300 mg/kg, and valsartan 30 mg/kg Route and dosing frequency: Oral gavage/single	Aprocitentan ($\downarrow 29 \pm 6$ mmHg at 10 mg/kg) valsartan ($\downarrow 12 \pm 5$ mmHg at 30 mg/kg), and spironolactone ($\downarrow 20 \pm 5$ mmHg at 300 mg/kg) decreased BP in DOCA-salt rats. Coadministration of valsartan (30 mg/kg) with aprocitentan (10 mg/kg) decreased the MAP beyond the predicted additive value ($\downarrow 5 \pm 5$, $\downarrow 22 \pm 6$, and $\downarrow 29 \pm 4$ mmHg in valsartan, aprocitentan and combination of both, respectively), demonstrating a synergism between the two compounds. Coadministration of valsartan (30 mg/kg) with spironolactone (300 mg/kg) decreased the MAP to the predicted additive value ($\downarrow 4 \pm 2$, $\downarrow 14 \pm 4$ and $\downarrow 18 \pm 5$ mmHg in valsartan, aprocitentan and combination of both, respectively) of both compounds, demonstrating an additive effect between the two compounds. Aprocitentan and spironolactone, alone or in combination, decreased MAP without affecting HR.
Study no.: B-18.042 Study title: Effect of aprocitentan or Spironolactone alone or in Combination With Enalapril on Blood Pressure And Heart Rate In Conscious DOCA-salt Rats Species/Strain: Rat/Wistar (DOCA-salt) Number/sex/group: 9-10/male/group Dose: aprocitentan 10 mg/kg, spironolactone 300 mg/kg, and enalapril 10 mg/kg Route and dosing frequency: Oral gavage/single	Aprocitentan ($\downarrow 29 \pm 6$ mmHg at ≥ 100 mg/kg), enalapril ($\downarrow 13 \pm 3$ mmHg at ≥ 100 mg/kg) and spironolactone ($\downarrow 20 \pm 5$ mmHg at ≥ 100 mg/kg) decreased BP in DOCA-salt rats. Coadministration of enalapril with aprocitentan decreased the MAP to the predicted additive value ($\downarrow 5 \pm 2$, $\downarrow 22 \pm 3$, and $\downarrow 27 \pm 4$ mmHg in enalapril, aprocitentan and combination of both, respectively) of both compounds. Coadministration of enalapril with spironolactone decreased the MAP to the predicted additive value ($\downarrow 4 \pm 2$, $\downarrow 14 \pm 4$, and $\downarrow 17 \pm 4$ mmHg in enalapril, spironolactone and combination of both, respectively) of both compounds as well. No change in HR was observed in all treatment groups.
Study no.: B-18.068 Study title: Effect of aprocitentan or Spironolactone alone or in Combination With Amlodipine on Blood Pressure And Heart Rate In Conscious DOCA-salt Rats Species/Strain: Rat/Wistar (DOCA-salt) Number/sex/group: 4-9/male/group Dose: aprocitentan 10 mg/kg, spironolactone 300 mg/kg and amlodipine 1 mg/kg Route and dosing frequency: Oral gavage/single	Aprocitentan ($\downarrow 29 \pm 6$ mmHg at 10 mg/kg), amlodipine ($\downarrow 23 \pm 3$ mmHg at 3 mg/kg. 1 mg/kg was selected for coadministration study), and spironolactone ($\downarrow 20 \pm 5$ mmHg at 300 mg/kg) decreased BP. Coadministration of amlodipine with aprocitentan decreased the MAP to the predicted additive value ($\downarrow 14 \pm 5$, $\downarrow 18 \pm 4$, and $\downarrow 26 \pm 5$ mmHg in amlodipine, aprocitentan and combination of both, respectively) of the two compounds. Coadministration of amlodipine with spironolactone decreased the MAP to the predicted additive value ($\downarrow 8 \pm 3$, $\downarrow 14 \pm 4$, and $\downarrow 16 \pm 4$ mmHg in amlodipine, spironolactone, and combination of both, respectively) of the combination of both compounds as well. No significant change in HR was observed in combination experiments.

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Study	Findings
Study no.: B-22.047 Study title: Effect of aprocitentan in Combination With Triple Antihypertensive Therapy on Blood Pressure and Heart Rate in DOCA-Salt Rats Species/Strain: Rat/Wistar (DOCA salt) Number/sex/group: 6-8/male/group Dose: Dose evaluation: Exforge HCT (0.1/1.6/0.25 and 0.3/4.8/0.75 mg/kg (for amlodipine/ valsartan/ hydrochlorothiazide, respectively)) Coadministration doses: Exforge HCT 0.2/3.2/0.5 mg/kg or Exforge HCT 0.2/3.2/0.5 mg/kg and aprocitentan 10 mg/kg Route and Dosing Frequency: Oral gavage/single	Coadministration of aprocitentan with Exforge HCT decreased the MAP to a greater extent than Exforge HCT alone (22±4 vs. 9±3 mmHg, respectively), demonstrating an additional effect of aprocitentan on top of Exforge HCT. No significant change in HR was observed following individual administration of vehicle, aprocitentan or Exforge HCT. A slight and transient HR increase was observed in rats coadministered with aprocitentan and Exforge HCT.
Study no.: B-14.051 Study title: Effect of ACT-132577 and Valsartan Alone or in Combination on Blood Pressure and Heart Rate in Conscious Spontaneously Hypertensive Rats Species/strain: Rat/SHR Number/sex/group: 6-18/male/group Dose: aprocitentan 100 mg/kg, valsartan 10 mg/kg Route and Dosing Frequency: Oral gavage/single	Aprocitentan (↓18±4 mmHg at 100 mg/kg) and valsartan (↓17±2 mmHg at 10 mg/kg) both decreased BP in SHR without affecting HR. Coadministration of aprocitentan with valsartan decreased MAP (↓17±3, ↓15±3, and ↓30±5 mmHg in valsartan, aprocitentan and combination of both, respectively) beyond the expected additive effect, demonstrating a synergism between the two molecules. No change in HR was observed.
Study no.: B-14.043 Study title: Effect of aprocitentan or Spironolactone Alone or in Combination with Enalapril on Blood Pressure and Heart Rate in Conscious Spontaneously Hypertensive Rats Species/strain: Rat/SHR Number/sex/group: 3-10/male/group Dose: aprocitentan 100 mg/kg, enalapril 10 mg/kg and spironolactone 10, 30, 100 and 300 mg/kg Route and dosing frequency: Oral gavage/single	Aprocitentan (↓18±4 mmHg at 100 mg/kg), enalapril (↓12±4 mmHg at 3 mg/kg), and spironolactone (↓12±3 mmHg at 300 mg/kg) decreased blood pressure in spontaneously hypertensive rats. Coadministration of enalapril with aprocitentan decreased the MAP beyond the predicted additive value (↓12±3, ↓14±2, and ↓26±4 mmHg in enalapril, aprocitentan and combination of both, respectively) demonstrating a synergism between the two compounds. Coadministration of enalapril with spironolactone decreased the MAP to the predicted additive value (↓17±4, ↓12±4, and ↓27±4 mmHg in enalapril, spironolactone and combination of both, respectively) of both compounds. Except for a moderate HR increase in enalapril-treated rats, no change in HR was observed in the other treatment groups.

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Study	Findings
Study no.: B-18.069 Study title: Effect of aprocitentan or Spironolactone alone or in Combination With Amlodipine on Blood Pressure And Heart Rate In Conscious Spontaneously Hypertensive Rats Species/strain: Rat/SHR Number/sex/group: 5-8/male/group Dose: aprocitentan 100 mg/kg, spironolactone 300 mg/kg, and amlodipine 2 mg/kg Route and dosing frequency: Oral gavage/single	Aprocitentan ($\downarrow 18 \pm 4$ mmHg at 100 mg/kg) and amlodipine ($\downarrow 23 \pm 3$ mmHg at 10 mg/kg, 2 mg/kg was selected for coadministration study) and spironolactone ($\downarrow 12 \pm 3$ mmHg at 300 mg/kg) decreased BP. Coadministration of amlodipine with aprocitentan decreased the MAP to the predicted additive value ($\downarrow 21 \pm 4$, $\downarrow 17 \pm 3$, and $\downarrow 29 \pm 4$ mmHg in amlodipine, aprocitentan and combination of both, respectively) of the two compounds, demonstrating an additive effect between the two compounds. Coadministration of amlodipine with spironolactone decreased the MAP to a lesser extent than the predicted additive value ($\downarrow 22 \pm 4$, $\downarrow 17 \pm 3$, and $\downarrow 20 \pm 4$ mmHg in amlodipine, spironolactone, and combination of both, respectively) of both compounds. Administration of amlodipine increased HR alone and in combination with aprocitentan or spironolactone.
Study no.: B-19.002 Study title: Effect of Spironolactone Alone or in Combination with Valsartan on Blood Pressure And Heart Rate in Conscious Spontaneously Hypertensive Rats Species/strain: Rat/SHR Number/sex/group: 6/male/group. Dose: Valsartan 10 mg/kg and spironolactone 300 mg/kg Route and dosing frequency: Oral gavage/single	Valsartan ($\downarrow 17 \pm 2$ mmHg at 10 mg/kg) and spironolactone ($\downarrow 12 \pm 3$ mmHg at 300 mg/kg) decreased blood pressure without affecting heart rate. Coadministration of valsartan with spironolactone decreased the MAP to the predicted additive value ($\downarrow 20 \pm 3$, $\downarrow 13 \pm 3$, and $\downarrow 27 \pm 2$ mmHg in valsartan, spironolactone, and combination of both, respectively) of both compounds, demonstrating an additive effect between the two compounds. No change in HR was observed.

Source: Pharmacology/toxicology reviewer-generated table base on Study Reports B-15.067, B-18.042, B-18.068, B-22.047, B-14.051, B-14.043, B-18.069, and B-19.002, Abbreviations: $\downarrow$, decrease; BP, blood pressure; DOCA, deoxycorticosterone acetate; HCT, hydrochlorothiazide; HR, heart rate; MAP, mean arterial pressure; No, number; SHR, spontaneously hypertensive rat

The effects of various treatment combinations with aprocitentan on blood pressure are summarized in the table below. In DOCA-salt rats, coadministration of aprocitentan and valsartan decreased MAP beyond a value predicted by an assumption of additive behavior, demonstrating synergism between the two compounds. In contrast, spironolactone combined with valsartan produced a purely additive effect. Coadministration of aprocitentan with enalapril demonstrated synergy in SHR but simple additive effects in DOCA-salt rats. Aprocitentan and amlodipine combination produced additive effects in SHR and DOCA-salt rats. Overall, these combination studies demonstrated that the addition of aprocitentan may be anticipated to have an additive to synergistic impact on blood pressure (BP) reduction when coadministered with other antihypertensive drugs.

Table 45. ABC Values of Single-Dose Combination Studies With Aprocitentan, Spironolactone, and Other Antihypertensive Drugs on Blood Pressure in SHR and DOCA-Salt Rats

	SHR		DOCA-salt rat	
	Aprocitentan 100 mg/kg	Spironolactone 300 mg/kg	Aprocitentan 10 mg/kg	Spironolactone 300 mg/kg
Valsartan 10 mg/kg	A: -662 ± 52 V: -407 ± 61 A+V: -1958 ± 248 ^a	S: -441 ± 35 V: -543 ± 50 S+V: -933 ± 78	Valsartan 30 mg/kg A: -543 ± 111 V: -31 ± 52 A+V: -887 ± 146 ^a	S: -270 ± 69 V: -28 ± 17 S+V: -389 ± 71
Enalapril 3 mg/kg	A: -838 ± 82 E: -168 ± 41 A+E: -1504 ± 162 ^a	S: -634 ± 121 E: -230 ± 58 S+E: -1013 ± 81	Enalapril 10 mg/kg A: -775 ± 98 E: -27 ± 32 A+E: -939 ± 176	S: -304 ± 86 E: -37 ± 25 S+E: -319 ± 76
Amlodipine 2 mg/kg	A: -1044 ± 68 Am: -177 ± 46 A+Am: -1074 ± 144	S: -813 ± 130 Am: -262 ± 108 S+Am: -682 ± 205	Amlodipine 3 mg/kg / 1 mg/kg ^b A: -685 ± 142 Am: -148 ± 62 A+Am: -1011 ± 119	S: -275 ± 103 Am: -97 ± 25 S+Am: -491 ± 68

^a indicates a synergistic effect on ABC. ^b 3 mg/kg was used with aprocitentan and 1 mg/kg was used with spironolactone.

Data represent the ABC (in mmHg·h) determined after single-dose administration, alone and in combination. Negative values indicate a reduction in blood pressure from baseline values. Data are expressed as mean ± SEM. The letter represents the compound tested. A = aprocitentan; ABC = area between the curves; Am = amlodipine; E = enalapril; S = spironolactone; SEM = standard error of the mean; SHR = spontaneously hypertensive rats; V = valsartan.

Source: Applicant-generated table (Table 3) from Pharmacology Written Summary.

Abbreviations: A, aprocitentan; ABC, area between the curves; Am, amlodipine; DOCA, deoxycorticosterone acetate; E, enalapril; S, spironolactone; SEM, standard error of the mean; SHR, spontaneously hypertensive rat; V, valsartan

13.1.1.2. Secondary Pharmacology

In an off-target screening assessment (Study No: T-15.025), the potential for interaction with 53 known receptor systems or enzymes was assessed. Aprocitentan (10µM) did not produce any noteworthy effects (defined as >50% inhibition or stimulation) in any of these assays.

13.1.1.3. Safety Pharmacology

A battery of safety pharmacology assessments (central nervous system, cardiovascular, and respiratory endpoints) was conducted, and no significant safety concerns were identified. Decreased BP and a compensatory increase in heart rate, which is considered related to the

desired primary pharmacological effect of aprocitentan, were observed. Results of these studies are summarized in the table below.

Table 46. Safety Pharmacology Studies

Study/Study No.	Key Findings
Study no.: T-18.063 Study title: ACT-132577: Effect on hERG Tail Currents Recorded from Stably Transfected HEK293 Cells at Near Physiological Temperature Cells/strain: Human embryonic kidney cells (HEK293)/stably expressed recombinant hERG channels (hERG/Ikr) Concentration: 3, 10, 30 and 100µM	• hERG tail current amplitude was reduced by more than 50% at 30µM and 100µM. • The IC₅₀ and IC₂₀ values were determined as 28.6µM and 7.2µM, respectively.
Study no.: T-14.027 Study title: ACT-132577E–Irwin Profile Test in the Rat After Single Oral Administration Species/strain: Wistar rats: CrI: WI (Han) Number/sex/group: 6/male/group Dose: 10, 50, and 150 mg/kg/day Route of administration/dosing frequency: Oral gavage/single dose NOEL: 150 mg/kg	• Behavioral and neurological signs were assessed up to 24 h after dosing. • No relevant effect on spontaneous activity; central nervous system excitability; autonomic functions, gait and muscle tone, and motor and sensory reflexes; or body temperature in the rat at any dose.
Study no.: T-14.028 Study title: ACT-132577E–Respiratory Function Evaluation in the Conscious, Freely Moving Rat by Whole Body Plethysmography Method After Single Oral Administration Species/strain: Wistar rats: CrI: WI (Han). Number/Sex/Group: 8/male/group Dose: 10, 50, and 150 mg/kg/day Route of administration and dosing/frequency: Oral gavage/single dose NOAEL: 150 mg/kg	• No alterations of respiratory parameters (respiratory rate, tidal volume, minute volume, inspiratory time, expiratory time, relaxation time, peak inspiratory flow, peak expiratory flow, and Penh (enhanced pause)) were observed.
Study no.: T-14.029 Study title: ACT-132577–Effects on Arterial Blood Pressure, Heart Rate, and Electrocardiogram, Following Oral (Capsule) Administration in the Conscious Beagle Dog Monitored by Telemetry Species/strain: Beagle dogs Number/sex/group: 3/sex/group Dose: 10, 75, and 250 mg/kg/day Route of administration and dosing/frequency: Oral gavage (capsule)/single dose (crossover design, minimum 3 days' washout period) NOAEL: 250 mg/kg	• All doses: A statistically significant decrease in systolic, diastolic, and mean arterial blood pressure in the range of 7 to 16 mmHg was observed, which is in line with expected pharmacodynamic effects. • All doses: HR was increased in the range of 8 to 17 bpm, which is considered as a compensatory effect for the decreased in arterial blood pressure. • No effect on atrioventricular and intraventricular conduction velocities, RR and PR intervals, or the duration of the QRS complex at any dose. • No effect on either QT or QTc intervals, indicating no effect on ventricular repolarization.

Source: Pharmacology/toxicology reviewer-generated table base on Study Reports T-18.063, T-14.027, T-14.028, and T-14.029
Abbreviations: h, hour; hERG, human ether-a-go-go related gene; HEK, human embryonic kidney; HR, heart rate; IC₂₀, inhibitory concentration causing 20 percent effect; IC₅₀, half maximal inhibitory concentration; Ikr, rapidly delayed rectifier; no., number; NOAEL, no observed adverse effect level; NOEL, no observed effect level

13.1.2. Pharmacokinetics/ADME/Toxicokinetics

General pharmacokinetic (PK) assessments, including absorption, distribution, metabolism, and excretion (ADME), and toxicokinetic evaluations with aprocitentan were conducted in rodents (rats) and nonrodents (rabbits and dogs) following oral (PO) or intravenous (IV) administration. The species and strains were those used in the toxicology program. Overall, the animal data predicted the PK/ADME profile in humans and no significant limitations on the interpretability of animal toxicology studies for predicting human safety were identified.

Absorption

Single-dose PK studies were conducted in male rats (0.5 mg/kg, IV or 3 mg/kg, PO) (B-05.130) and dogs (0.3 mg/kg, IV or 3 mg, PO) (B-13.249) by administering the (b) (4) form of aprocitentan. PK parameters are summarized in the tables below. Aprocitentan was identified as a low-clearance drug in rats (1.3 mL/min.kg) and dogs (0.4 mL/min.kg). In rats, oral absorption was slow with a median time to maximum concentration (T_{max}) of 8 h and oral bioavailability was 41% ((b) (4) form in suspension). The slow uptake observed in this assessment was likely due to poor solubility and/or slow dissolution of the drug substance. In dogs when administered with a more clinically relevant (b) (4) aprocitentan, oral bioavailability was ~90% and the T_{max} was 3 hours.

Table 47. Pharmacokinetic Parameters in Wistar Rats and Beagle Dogs (Single Intravenous Administration)

Species	Wistar rat (n = 6, male), Beagle dog (n = 4, male)		
Administration	Rat: 0.5 mg/kg; solution in 55% 50 mM Tris (pH 8.3) / 45% PEG400 Dog: 0.3 mg/kg; solution in 70% 50 mM Tris (pH 8.3) / 30% PEG400		
Species	Parameter	Geometric mean	Range
Rat (0.5 mg/kg) [B-05.130]	AUC _{0-inf} (ng·h/mL)	6660	5200–7960
	CL (mL/min·kg)	1.3	1.0–1.6
	V _{ss} (L/kg)	1.0	0.8–1.3
	t _{1/2} (h)	8.7	8.2–9.2
Dog (0.3 mg/kg) [B-13.249]	AUC _{0-inf} (ng·h/mL)	12,000	6330–20,100
	CL (mL/min·kg)	0.4	0.3–0.8
	V _{ss} (L/kg)	0.3	0.2–0.3
	t _{1/2} (h)	7.3	5.3–11

Source: Applicant-generated table (Table 1) from Pharmacokinetic Written Summary
Abbreviations: AUC_{0-inf}, area under the concentration-time curve extrapolated from 0 hour to infinity; CL, systemic plasma clearance; n, number; PEG, polyethylene glycol; t_{1/2}, apparent terminal half-life; Tris, tris(hydroxymethyl)aminomethane; V_{ss}, volume of distribution at steady-state

No difference in the rate or extent of oral absorption was observed for (b) (4) in (b) (4) capsules, (b) (4) capsules and the (b) (4) form in (b) (4) capsules in dogs (geometric mean area under the concentration-time curve [AUC]_{0-t} of 8860, 9100, 9030 ng·h/mL, respectively and maximum plasma concentration [C_{max}] of 737, 766 and 785 ng/mL, respectively).

Table 48. Pharmacokinetic Parameters in Wistar Rats and Beagle Dogs (Single Oral Administration)

Species	Wistar rat (n = 6, male), Beagle dog (n = 4, male)		
Administration	Rat: 3 mg/kg; suspension in 7.5% gelatin Dog: 3 mg total dose in capsules (0.22–0.33 mg/kg)		
Rat [B-05.130]			
Design	Parameter	Geometric mean	Range
(b) (4), suspension in 7.5% gelatin, fed state	AUC _{0-last} (ng·h/mL)	16,300	12,900–19,300
	C _{max} (ng/mL)	708	465–1040
	t _{max} (h)	8.0 ^a	6.0–24
	F (%) ^b	41	–
Dog [B-13.249]			
(b) (4) capsules, fasted state	AUC _{0-last} (ng·h/mL)	9100	5710–20,900
	C _{max} (ng/mL)	766	588–1180
	t _{max} (h)	2.7 ^a	2.0–3.0
	F (%) ^c	92	71–118
(b) (4) capsules, fasted state	AUC _{0-last} (ng·h/mL)	8860	5080–22,800
	C _{max} (ng/mL)	737	508–1260
	t _{max} (h)	3.2 ^a	3.0–4.0
	F (%) ^c	88	71–105

^a Median;

^{b,c} Oral bioavailability calculated with reference to the AUC_{0-inf} at an intravenous dose of ^b 0.5 mg/kg (6660 ng·h/mL) / ^c 0.3 mg/kg (12,000 ng·h/mL).

Source: Applicant-generated table (Table 2) from Pharmacokinetics Written Summary

Abbreviations: AUC_{0-last}, area under the concentration-time curve from 0 hour to last measurable timepoint; C_{max}, maximum plasma concentration; F, oral bioavailability; n, number; t_{max}, time to reach maximum plasma concentration

In male DOCA-salt rats, a model of hypertension, administration of aprocitentan (0.3 to 300 mg/kg) showed dose-proportional increases in exposure (AUC_{0-t} and C_{max}) at dose levels 0.3 to 30 mg/kg and a less than dose-proportional increase in exposures at dose levels 100 to 300 mg/kg.

Table 49. Dose-Proportionality of Aprocitentan Exposure in Male DOCA-Salt Sensitive Rats (Single Oral Administration)

Dose (mg/kg)	AUC _{0-t} (µg·h/mL)	AUC _{0-t} /Dose (µg·h/mL)/(mg/kg)	C _{max} (µg/mL)	C _{max} /Dose (µg/mL)/(mg/kg)	t _{max} (h)
0.3	1.83 (1.24–2.24)	6.1	0.16 (0.10–0.20)	0.5	3 (3–3)
1	7.40 (7.07–8.09)	7.4	0.62 (0.47–0.78)	0.6	3 (2–8)
3	21.9 (17.2–26.6)	7.3	2.42 (2.18–2.59)	0.8	3 (2–3)
10	67.1 (54.5–88.2)	6.7	5.49 (4.88–6.37)	0.5	4 (3–8)
30	165 (157–177)	5.5	14.0 (12.5–16.5)	0.5	4 (2–6)
100	271 (135–468)	2.7	26.5 (22.4–35.7)	0.3	6 (4–6)
300	613 (503–817)	2.0	42.1 (41.0–44.1)	0.1	4 (3–6)

Data presented are geometric means (range) of n = 3/group/time point; t_{max} is given as median (range).

Source: Applicant-generated table (Table 3) from Pharmacokinetics Written Summary

Abbreviations: AUC_{0-t}, area under the concentration-time curve from 0 hour to time t of the last measured concentration above limit of quantification; C_{max}, maximum plasma concentration; DOCA, deoxycorticosterone acetate; h, hour; t_{max}, time to reach maximum plasma concentration

In repeat-dose (4-week) toxicity studies (T-14.022, T-14.023), a sex difference in aprocitentan PK was observed in rats but not in dogs. The AUC₀₋₂₄ values in female rats were 20–60% higher than those of males.

Table 50. Sex Differences in Aprocitentan Exposure in Rats and Dogs

Species	Dose (mg/kg)	AUC ₀₋₂₄ (µg·h/mL)	
		Males	Females
Rat ^a [T-14.023]	10	114	153
	50	552	865
	250	3890	4800
Dog ^b [T-14.022]	75	1980 (1810–2280)	1770 (855–2600)
	250	2520 (1900–3160)	2830 (1290–3800)
	1000	4540 (3650–5400)	5220 (4590–6020)

^a Data presented are geometric means from Day 1 of the 4-week toxicity studies with n = 3/group (composite profiles) in rats.

^b Data presented are geometric means and range of n = 4/group in dogs (individual profiles).

Source: Applicant-generated table (Table 4) from Pharmacokinetics Written Summary

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from 0 hour to 24 hours after dosing

Distribution

The volume of distribution (Vd) of aprocitentan was determined in rats (0.5 mg/kg, IV) (B-05.130) and dogs (0.3 mg/kg, IV) (B-13.249). The mean Vd_{ss} was 1.0 L/kg in the rat and 0.3 L/kg in the dog, which approximates total body water volume.

The tissue distribution of aprocitentan (0.3 mg/kg, P.O, ¹⁴C-radiolabel) was evaluated in male albino Wistar rats (for 10 days) and pigmented Lister Hooded rats (for 15 days) using quantitative whole-body autoradiography (B-14.029). Absorption and distribution of radioactivity into tissues were similar in both strains. The liver, kidney cortex, lung, pituitary, thyroid, and myocardium showed the highest exposures, with peak exposures observed at 8 hours postdose. No relevant retention of radioactivity in the uveal tract/retina, pigmented skin, or meninges of the brain was observed at any time point.

Binding of aprocitentan (¹⁴C-radiolabel, 0.1–300 µg/mL) to plasma proteins was measured in mouse, rat, rabbit, dog, and human plasma using equilibrium dialysis (B-07.077). High plasma protein binding (>98%) was observed in all species, with a free fraction between 0.1% to 0.5% (Table 51).

Table 51. Plasma Protein Binding of Aprocitentan in Different Species

Species	Fraction bound (%)	Free fraction (%)
Mouse	99.0	1.0
Rat	98.7	1.3
Rabbit	99.9	0.1
Dog	98.3	1.7
Human	99.5	0.5

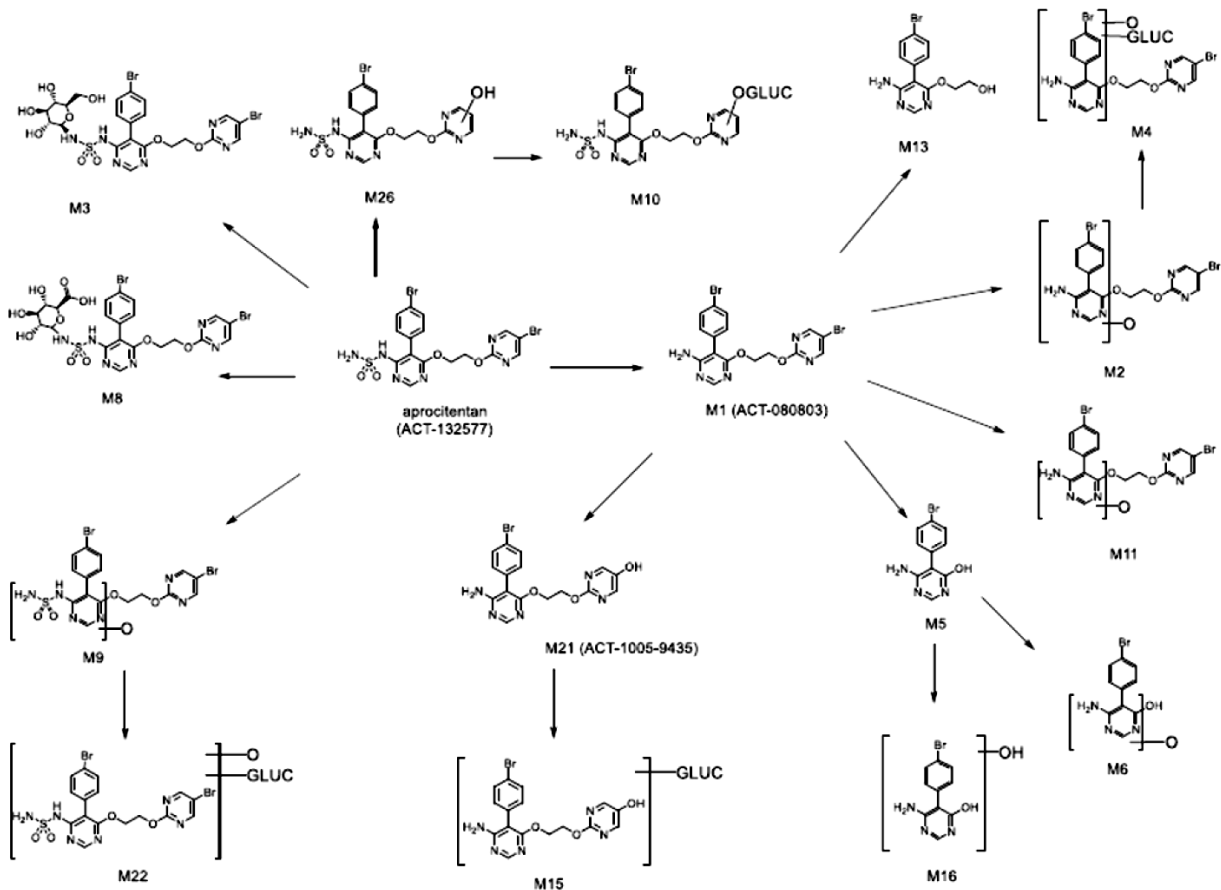
Source: Applicant-generated table (Table 6) from Pharmacokinetics Written Summary.

Partitioning into red blood cells was assessed in Study B-07.077. Mean blood/plasma ratios were observed in the range of 0.54 to 0.69 for all species, indicating that aprocitentan has limited ability to partition into red blood cells.

Metabolism

Metabolite structure was evaluated in vitro using rat and human hepatocytes, bile using bile duct-cannulated rats, and in urine. Aprocitentan was heavily metabolized along five different pathways, producing a total of 15 metabolites that were characterized, as shown in [Figure 14](#).

Figure 14. Metabolic Pathways of Aprocitentan



Source: Applicant-generated figure (Figure 1) from Pharmacokinetics Written Summary
Abbreviation: GLUC, glucuronic acid

In a cross-species comparison study (B-14.033) using liver microsomes and hepatocytes of human/animal species, the metabolite profile of aprocitentan (^{14}C -radiolabeled ACT-132577B) was compared between species as shown in the following table. The metabolic profile was characterized using either liver microsomes (B-14.050) or hepatocytes (B-14.034) of mouse, rat, rabbit, dog, cynomolgus monkey and human.

Table 52. Cross-Species Comparison of the Aprocitentan Metabolic Profiles

Species	In vitro system	M1	M2	M3	M4	M5	M6	Σ metabolites	ACT-132577B
Human	Liver microsomes	4.3	2.1	ND ^a	ND	ND	ND	6.4	94
	Hepatocytes ^a	3.8–15	3.0–7.6	4.0	3.6	1.7–2.1	4.5	15–21	79–85
Rat	Liver microsomes	5.1	1.4	ND	ND	1.5	ND	10 ^b	90
	Hepatocytes	5.8	1.8	2.6	2.0	5.3	3.9	32 ^c	68
Dog	Liver microsomes	4.7	1.7	ND	ND	1.3	ND	9.3 ^d	91
	Hepatocytes	6.8	8.4	ND	ND	5.5	ND	23 ^e	77
Cynomolgus monkey	Liver microsomes	3.7	2.8	ND	ND	ND	ND	8.0 ^f	92
	Hepatocytes	3.9	3.9	ND	ND	ND	ND	18 ^g	83
Rabbit	Liver microsomes	5.6	2.3	ND	ND	ND	ND	7.9	92
	Hepatocytes	4.3	ND	ND	ND	ND	ND	4.3	96
Mouse	Liver microsomes	5.1	2.1	ND	ND	ND	ND	7.2	93
	Hepatocytes	3.8	13	1.4	5.3	1.9	ND	27 ^h	73
Controls	Without microsomes	9.3	ND	ND	ND	ND	ND	9.3	91
	Microsomes without NADPH	6.4	ND	ND	ND	ND	ND	6.4	94
	Without hepatocytes	8.7	ND	ND	ND	ND	ND	8.7	91

All values are expressed as percent of total chromatogram radioactivity; metabolites with an abundance of < 0.1% are not listed.

^a Data are from three different batches of human hepatocytes; range indicates the presence of a metabolite in more than one hepatocyte batch.

^b Includes the non-human metabolite M9 (2.0%)

^c Includes the non-human metabolites M8 (6.9%) and M9 (3.6%)

^d Includes the non-human metabolite M20 (1.6%)

^e Includes the non-human metabolite M14 (2.3%)

^f Includes the non-human metabolite M20 (1.5%)

^g Includes the non-human metabolite M19 (5.9%) and M28 (3.8%)

^h Includes the non-human metabolite M11 (1.2%)

Source: Applicant-generated table (Table 7) from Pharmacokinetics Written Summary
Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate; ND, not detected

All human metabolites were detected in the rat and/or the dog. No disproportionate human metabolites were identified.

In the repeated dose rat and dog toxicity studies, aprocitentan increased the mRNA expression of cyp3a1, cyp2b1, cyp2b2, ugt1a1, ugt1a6 and ugt2b1 (B-17.046) in rats and cyp2A12 mRNA in dogs (B-17.047) in a dose-dependent manner, indicating a species-specific enzyme induction in liver.

Excretion

The major excretion pathway for aprocitentan in rats was identified as biliary based on a study in bile duct-cannulated rats. In this study, oral (3 mg) or intravenous (1 mg) administration of aprocitentan (¹⁴C-labeled ACT-132577B) accounted for 50% of total oral dose and 70% of total intravenous dose recovered in bile. Renal excretion represented 16% and 14% of total dose for the oral and intravenous routes, respectively. Approximately 30% of the total oral dose and 22% of total intravenous dose was recovered in feces (B-14.034). At 72 hours, the mean total recovery was approximately 90% of the total drug exposure for the oral route and complete elimination of the drug was measured following intravenous administration.

No milk excretion studies were conducted with aprocitentan; however, aprocitentan was consistently observed in milk samples across all time points after oral administration of ¹⁴C-labeled macitentan (B-11.837 Annex) in rats.

Toxicokinetics

In repeat-dose oral studies, systemic exposure generally increased in a dose-dependent manner in both rats and dogs. The exposure was decreased at the end of the dosing period in rats compared to Day 1. The toxicokinetic parameters in the pivotal toxicology studies are summarized in the table below.

Table 53. Toxicokinetic Data

Study/Study No.	TK Parameters								
<i>General Toxicology Studies</i>									
Study no: T-14.036	TK Parameters for the Wistar Rat at Week 26								
Study title: ACT-132577E: 26-Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 9-Week Treatment-Free Period	Dose (mg/kg/day)	Week	Sex	Tmax (h)	Cmax (ng/mL)	AUC0-24h (h*ng/mL)	Tlast (h)	Cmax/D (ng/mL)/(mg/kg)	AUC0-24h/D (h*ng/mL)/(mg/kg)
Sample collection times: 1, 2, 4, 7, 12 and 24 h postdose on Day 1 and Week 26	0	1	f	7	2.74	44.3	24	-	-
Accumulation: Exposure was lower in Week 26 compared to Week 1.	0	1	m	4	1.16	2.32 [#]	4	-	-
Sex differences: Females have higher exposure than males (female to male ratio of 1.1 to 1.8).	0	26	f	7	19.3	227	24	-	-
NOAEL: 50 mg/kg/day	0	26	m	7	14.1	125	24	-	-
	10	1	f	2	22900	205000	24	2300	20000
	10	1	m	1	23300	194000	24	2300	19000
	10	26	f	1	22000	138000	24	2200	14000
	10	26	m	1	17200	76900	24	1700	7700
	50	1	f	2	159000	1770000	24	3200	35000
	50	1	m	4	127000	1290000	24	2500	26000
	50	26	f	1	138000	789000	24	2800	16000
	50	26	m	1	96100	448000	24	1900	9000
	100	1	f	4	252000	3530000	24	2500	35000
	100	1	m	4	220000	2780000	24	2200	28000
	100	26	f	1	217000	1870000	24	2200	19000
	100	26	m	1	205000	1130000	24	2100	11000
	250	1	f	7	310000	6050000	24	1200	24000
	250	1	m	7	284000	5170000	24	1100	21000
	250	26	f	4	337000	3080000	24	1300	12000
	250	26	m	2	240000	1710000	24	960	6800

[#]AUC0-4h

Source: Applicant-generated table from Study Report T-14.036

Study/Study No.

Study no: T-16.021
Study title: ACT-132577E: 26-Week Toxicity Study by the Oral Route (Gavage) in the Male Rat Followed by a 9-Week Treatment-Free Period
Sample collection times: 1, 2, 4, 7, 12 and 24 h postdose on Day 1 and Week 26
Accumulation: Exposure was lower in Week 26 compared to Week 1.
NOAEL: 50 mg/kg/day

TK Parameters

TK Parameters for the Wistar and SD Rat at Week 26

Strain: Wistar

Dose (mg/kg/day)	Day/Week	Tmax (h)	Cmax (ng/mL)	AUC _{0-24h} (h*ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUC _{0-24h} /D (h*ng/mL)/(mg/kg)
10	D1	4	19600	224000	2000	22000
10	W4	1	21700	121000	2200	12000
10	W13	1	18600	97000	1900	9700
10	W26	1	19500	105000	2000	11000
50	D1	7	128000	1770000	2600	35000
50	W4	1	67700	360000	1400	7200
50	W13	1	110000	589000	2200	12000
50	W26	2	70200	554000	1400	11000
250	D1	4	288000	5820000	1200	23000
250	W4	7	148000	1560000	590	6200
250	W13	2	159000	1800000	640	7200
250	W26	4	158000	1460000	630	5800

Strain: Sprague Dawley

Dose (mg/kg/day)	Day/Week	Tmax (h)	Cmax (ng/mL)	AUC _{0-24h} (h*ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUC _{0-24h} /D (h*ng/mL)/(mg/kg)
10	D1	2	20400	193000	2000	19000
10	W4	1	18800	109000	1900	11000
10	W13	2	17300	96500	1700	9600
10	W26	2	21100	119000	2100	12000
50	D1	7	121000	1540000	2400	31000
50	W4	1	70000	460000	1400	9200
50	W13	4	54900	367000	1100	7300
50	W26	1	70000	474000	1400	9500
250	D1	12	250000	5080000	1000	20000
250	W4	12	148000	1960000	590	7900
250	W13	4	149000	1810000	600	7200
250	W26	2	106000	1440000	420	5800

Source: Applicant-generated table from Study Report T-16.021

Study no: T-15.053

Study title: ACT-132577: 39-Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 13-Week Treatment-Free Period
Sample collection times: 1, 2, 4, 7, 12 and 24 h postdose on Day 1 and Week 13.
Exposure: Dose proportional on Day 1 and less than dose proportional on Week 36
Accumulation: Exposure was slightly higher in Week 39 compared to Week 1.
NOAEL: 5 mg/kg/day

TK Parameters for Dogs at Week 39

Dose (mg/kg/day)	Day/Week	Sex	T _{max} [#] (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	C _{max} /D (ng/mL)/(mg/kg)	AUC _{0-24h} /D (h*ng/mL)/(mg/kg)
0	Day 1	f	-	-	-	-	-
0	Week 39	f	5.5	2.20	35.7 ^{###}	-	-
0	Day 1	m	4	1.85	14.9 ^{###}	-	-
0	Week 39	m	4	2.93	57.5	-	-
5	Day 1	f	2	17800	235000	3600	47000
5	Week 39	f	4	26900	406000	5400	81000
5	Day 1	m	3	14600	196000	2900	39000
5	Week 39	m	2	24700	342000	4900	68000
25	Day 1	f	3	72400	1230000	2900	49000
25	Week 39	f	4	108000	1860000	4300	74000
25	Day 1	m	2	60100	946000	2400	38000
25	Week 39	m	4	106000	1810000	4200	72000
50	Day 169	f	4	139000	2450000	2800	49000
50	Week 39	f	7	162000	2960000	3200	59000
50	Day 171	m	4	124000	2180000	2500	44000
50	Week 39	m	4	149000	2700000	3000	54000
75	Day 1	f	7	144000	2670000	1900	36000
75	Day 162	f	7	185000	3580000	2500	48000
75	Day 1	m	4	136000	2560000	1800	34000
75	Day 164	m	7	171000	3170000	2300	42000

[#] presented as median

^{###} AUC_{0-10h}

^{###} One out of six AUCs was AUC_{0-10h} (for detail see Table 2)

Source: Applicant-generated table from Study Report T-15.053

Reproductive Toxicology Studies

Study no: T-16.001

Study title: ACT-132577E: Fertility Toxicity Study by the Oral Route (Gavage) in the Male Rat (Segment I)
Doses: aprocitentan 5, 25, 250 mg/kg/day
Sample collection times: 1, 2, 4, 6, 10 and 24 hours on Days 6 and 17
Exposure: Approximately dose-proportional
Accumulation: Lower in Week 15 compared to Day 1

TK Parameters for the Male Rats at Week 1 and Week 13

Dose (mg/kg/day)	Week	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)
5	1	5	12500	181000
5	13	6.25	16100	239000
25	1	6.25	55700	935000
25	13	6.25	70600	1280000
50	1	5.5	86000	1500000
50	13	6.25	104000	1850000
250	1	10	176000	3560000
250	13	3 ^{##}	119000 ^{##}	2130000 ^{##}

[#] Arithmetic mean calculated using rounded mean values of data obtained from Table 3 of the Toxicokinetic Report.

^{##} Animal 23 excluded since this dog had AUC_{0-7h} instead of AUC_{0-24h}

Source: Applicant-generated table from Study Report T-16.001

Study/Study No.

TK Parameters

NOAEL: 5 mg/kg/day

Study no: T-16.002

Study title: ACT-132577E: Fertility

Toxicity Study by the Oral Route
(Gavage) in the Female Rat (Segment I).

Sample collection times: 1, 2, 4, 7, 12
and 24 h postdose on Day 1 and Week 7

NOAEL: 10 mg/kg/day

TK Parameters for the Female Rats at Day 1 and GD7

Dose (mg/kg/day)	Day	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	C _{max} /D (ng/mL)/ (mg/kg)	AUC _{0-24h} /D (h*ng/mL)/ (mg/kg)
10	D1	2	20500	233000	2100	23000
10	G7	1	17400	158000	1700	16000
50	D1	2	120000	1750000	2400	35000
50	G7	2	86700	788000	1700	16000
250	D1	12	324000	6770000	1300	27000
250	G7	12	242000	4040000	970	16000

Source: Applicant-generated table from Study Report T-16.002

Study no: T-12.804

Study title: ACT-064992: Oral (Gavage)
Embryo-Foetal Development Study in the
Rat with Toxicokinetic Sampling

Doses: Macitentan (ACT-0649920) 3, 10
and 150 mg/kg/day

Sample collection times: 1, 2, 4, 6, 10
and 24 hours on Days 6 and 17.

NOAEL: Not established (<3 mg/kg/day)

Rat EFD TK Parameters at GD 6 and GD 17

Dose level (mg/kg/day)	ACT-064992			ACT-132557		
	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)
Day 6 of gestation						
3	6	2050	31400	10	1490	28300
10	6	5140	80500	10	2850	51700
150	6	39100	548000	10	28100	479000
Day 17 of gestation						
3	4	2140	26500	6	1960	36800
10	4	6900	89500	6	4560	88600
150	4	34200	431000	6	33600	529000

Source: Applicant-generated table from Study Report T-12.804

Study no: T-05.029

Study title: ACT-064992: Preliminary
Embryo-Fetal Toxicity Study by Oral
Gavage Administration to Rabbits ^{(b) (4)}

Doses: Macitentan (ACT-0649920) 2.5,
12.5 and 25 mg/kg/day

Sample collection times: 1, 2, 4, 7, 10
and 24 hours on Days 6 and 17

NOAEL: Not established
(<2.5 mg/kg/day)

Rabbit EFD TK Parameters at GD 7 and GD 19

Macitentan Exposure

Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)	
	Day 6	Day 19	Day 6	Day 19
2.5	7.54	7.95	114	118
12.5	31.8	22.2	543	323
25	44.5	29.1	724	396

Aprocitentan Exposure

Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)	
	Day 6	Day 19	Day 6	Day 19
2.5	6.04	23.7	101	520
12.5	37.5	107	525	2280
25	72.1	206	982	4290

Source: Applicant-generated table from Study Report T-05.029

Study/Study No.

Study no: T-09.617
Study title: ACT-064992: Study for Effects on Pre- and Postnatal Development Including Maternal Function in the Wistar Rat
Sample collection times: Days 4 and 12 p.p. F0 Females–1, 4, 6, and 24 h and F1 pups–Day 4 and 12 p.p.
NOAEL: 50 mg/kg/day for dams and no NOAEL was established for reproduction parameters

TK Parameters

Pre- and Postnatal TK Parameters for the Rat at Day 4 and Day 12

Dams (F0 females)

Compound	Dose (mg/kg)	Post-Partum Day	Tmax (h)	Cmax (ng/mL)	AUC0-24h (h*ng/mL)	Cmax/D (ng/mL)/(mg/kg)	AUC0-24h/D (h*ng/mL)/(mg/kg)
ACT-064992	0	4	4	87.2	1200	NA	NA
	0	12	1	22.3	114 [#]	NA	NA
	10	4	4	6360	64500	640	6500
	10	12	4	6970	69100	700	6900
	50	4	4	16600	165000	330	3300
	50	12	4	14800	143000	300	2900
	250	4	6	37300	407000	150	1600
ACT-132577	0	12	6	30500	294000	120	1200
	0	4	6	27.4	548	NA	NA
	0	12	NA	NA	NA	NA	NA
	10	4	4	3270	51700	330	5200
	10	12	6	4380	69800	440	7000
	50	4	6	11800	164000	240	3300
	50	12	4	13400	185000	270	3700
ACT-373898	250	4	4	27800	382000	110	1500
	250	12	6	28800	375000	120	1500
	0	4	NA	NA	NA	NA	NA
	0	12	NA	NA	NA	NA	NA
	10	4	4	3.38	48.8	0.3	4.9
	10	12	4	3.25	60.0	0.3	6.0
	50	4	6	17.3	181	0.4	3.6
250	12	6	16.4	171	0.3	3.4	
	4	6	42.0	459	0.2	1.8	
	12	6	42.7	400	0.2	1.6	

[#] AUC0-6h. This value was used for calculation of ratios in the following tables.

Pups (F1)

Dose of Dam (mg/kg)	Post-Partum Day	Sex	ACT-064992				ACT-132577 [#]			
			Geometric Mean (ng/mL)	Min (ng/mL)	Max (ng/mL)	n	Geometric Mean (ng/mL)	Min (ng/mL)	Max (ng/mL)	n
10	4	f	13.3	11.2	15.4	3	458	369	539	4
10	4	m	10.9	10.9	10.9	1	500	434	577	2
10	12	f	34.7	27.9	43.3	4	1070	785	1300	4
10	12	m	32.8	28.7	37.7	4	1110	932	1360	4
50	4	f	52.1	52.1	52.1	1	1600	1600	1600	1
50	4	m	63.9	63.9	63.9	1	1430	1430	1430	1
50	12	f	111	104	130	4	3200	2160	4770	4
50	12	m	115	109	129	4	3110	2320	4680	4
250	4	f	140	97.5	225	3	3040	2690	3420	3
250	4	m	154	123	194	2	2710	2240	3270	2
250	12	f	329	295	349	3	6320	4930	7970	3
250	12	m	330	313	345	3	5880	4760	7310	3

[#] Concentrations of metabolite ACT-373898 in pups were BLQ at all maternal doses except one concentration of 1.31 ng/mL that was detected in pooled sample of female pups at a maternal dose of 250 mg/kg. This concentration was very close to the quantification limit of 1 ng/mL; therefore, this data was omitted in this table.

Source: Applicant-generated table from Study Report T-09.617

Source: Pharmacology/Toxicology reviewer generated table for all the above studies.

Abbreviations: AUC_{24h}, area under the concentration-time curve at 24 hours; AUC_{0-24h}, area under the concentration-time curve from 0 hour to 24 hours; C_{max}, maximum concentration; D, day; EFD, embryo-fetal development; f, female; F0, parental generation; F1, first generation of offspring or first filial generation; GD, gestational day; h, hour; m, male; max, maximum; min, minimum; n, no., number; NOAEL, no observed adverse effects level; p.p., pre- and postnatal; SD, Sprague-Dawley; TK, toxicokinetic; T_{last}, time of last measurable concentration, T_{max}, time to peak concentration, W, week

13.1.3. Toxicology

13.1.3.1. General Toxicology

Repeat dose toxicology studies were conducted in rats (up to 26 weeks) and dogs (up to 39 weeks). These animal species were considered relevant for human risk assessment because pharmacodynamic (PD) and PK/ADME profiles are similar to those in humans. Key results are summarized in the following subsections.

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TRYVIO (aprocitentan)

Aprocitentan ((b) (4), ACT132577) was administered in all repeated-dose toxicity studies in dogs, whereas aprocitentan (b) (4) (ACT-132577E) was administered in all rat general toxicity studies (except for a 2-week dose range finding study). The (b) (4) form (ACT132577E) produced approximately 6-fold higher exposure than to the (b) (4) at the same dose level in rats.

13.1.3.1.1. Repeat-Dose Toxicity Studies in Rats

Repeat-dose toxicity studies were conducted in rats for up to 26-weeks with oral dosing of 10 to 1000 mg/kg/day aprocitentan. Two 26-week toxicity studies were conducted with the aprocitentan (b) (4) form (10 to 250 mg/kg/day). The first study was conducted in Wistar rats. To further evaluate the thyroidal follicular hyperplasia and adenomas observation in the first study, a supplemental study was conducted only in male Wistar and Sprague Dawley (SD) rats. Key findings from each 26-week study are summarized in the table below.

26-Week (9-Week Recovery) Toxicology Studies

Study Number/Title: 8310210/ACT-132577E: 26 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 9 Week Treatment-Free Period

Key Study Finding

- Dose dependent increases in the incidence and severity of dark and enlarged liver was observed with an associated increase in organ weights due to hepatocellular hypertrophy. These changes were due to reversible microsomal enzyme induction, considered an adaptive response.
- At the highest dose of 250 mg/kg/day, adverse focal to multifocal centrilobular hydropic degeneration of hepatocytes were observed.
- Reversible follicular hypertrophy at ≥ 10 mg/kg/day and hyperplasia at ≥ 50 mg/kg/day in the thyroid glands were considered adaptive response as a consequence of increased hepatic metabolism. Follicular adenomas observed at doses ≥ 100 mg/kg/day in this study was not observed in the supplemental study at doses up to 250 mg/kg/day in male SD and Wistar rats for the same duration. The findings in the thyroid were not considered clinically relevant.
- The no observed adverse effect level (NOAEL) was determined to be 50 mg/kg/day (AUC_{0-24h} values of $619 \text{ h} \cdot \mu\text{g/mL}$, approximately 18-fold the AUC at the maximum recommended human dose [MRHD]), based on clinically irrelevant thyroid follicular adenomas at ≥ 100 mg/kg/day and multifocal hydropic degeneration of hepatocytes at 250 mg/kg/day.

Table 54. Study Information for Study Number 8310210/ACT-132577E

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 10, 50, 100 and 250 mg/kg and once daily
Route of administration (volume)	Oral Gavage (10 mL/kg/day).
Formulation/vehicle	Aqueous solution of 0.5% methylcellulose containing 0.5% Tween 80, in water
Species/strain	Rat/Wistar: Crl: WI (Han).

Study Features and Methods	Details
Number/sex/group	20 (main study), 5 (recovery) and 9 (toxicokinetic)/sex/strain/group
Age	6 to 7 weeks (main animals)
Satellite groups/unique design	9 (control or treated)/sex/group
Deviation from study protocol affecting interpretation of results	Reported deviations from study plan and SOP may not have any impact on the integrity of the study

Source: Pharmacology/toxicology reviewer generated table based on Study Report 8310210

Abbreviations: GLP, good laboratory practices; SOP, standard operating procedure

Table 55. Observations and Results for Study Number 8310210/ACT-132577E

Parameters	Major Findings
Mortality	One female animal in control group due to multiple clinical signs including abnormal respiration, protruding eyes and weight loss, and one male animal in 250 mg/kg/day group due to impaired mobility were sacrificed early. As no other animals showed a similar clinical observation at 250 mg/kg/day, the impaired mobility was not considered treatment related.
Clinical signs	Minor findings in the treatment groups were not considered adverse effects.
Body weights	Slight decrease in mean body weight gain was noted (-8.0% in male and -19% in female) at 250 mg/kg/day and no differences were noted during the recovery phase.
Ophthalmoscopy	No treatment-related adverse findings were observed.
Hematology	No treatment related changes were noted except a slight reduction in RBC, Hb and PCV (-7%).
Clinical chemistry	Dose-dependent increase in total protein in all the doses tested, with associated increase in globulin ≥ 100 mg/kg/day was observed in female animals. Cholesterol was increased in females at ≥ 100 mg/kg/day, and alanine aminotransferase was increased in males at 250 mg/kg/day. These changes were reversed at the 9-week recovery phase.
Gross pathology	Liver: Dose-dependent increase in dark and enlarged liver was noted at all the doses tested with increased severity with dose. It was not recovered in two females at 250 mg/kg/day. Kidney: Dose-dependent increase in dark kidney was mainly observed in female (except one male at 250 mg/kg/day) animals. It was not recovered in one female at 10 mg/kg/day and two females at 100 mg/kg/day and three females at 250 mg/kg/day. Thyroid glands: Dose dependent enlarged lobes were observed in thyroids.
Organ weights	Reversible dose dependent increase in organ absolute and/or relative weights (body weight and brain weight) were observed in liver (males ≥ 10 mg/kg/day and females ≥ 10 mg/kg/day), thyroid gland (≥ 100 mg/kg/day) and kidney (≥ 100 mg/kg/day).

Parameters	Major Findings
Histopathology Adequate battery: Yes	Liver: Dose-dependent increased incidence and/or severity of hepatocellular hypertrophy (centrilobular to diffuse, minimal to marked) was observed. These changes were fully reversible after the recovery period and were likely related to enzyme induction, hence, were considered adaptive response rather than adverse effects. At 250 mg/kg/day, a focal-to-multifocal hydropic degeneration of hepatocytes, mainly at a centrilobular location was observed, which was fully resolved at the end of recovery. The affected hepatocytes appeared swollen/ballooned with clear cytoplasm occasionally associated with increased apoptosis. Kidney: Brownish pigment was observed (males ≥ 50 mg/kg/day and females ≥ 10 mg/kg/day) in the tubular epithelia (localized mainly at proximal tubules in the outer cortex) with more incidences in females and it is not fully reversed. Thyroid glands: Follicular hypertrophy (males at ≥ 10 mg/kg/day and in females at ≥ 50 mg/kg/day) was observed. Follicular hyperplasia (distributed mainly diffusely, rarely focally as nodular hyperplasia) was observed in males and females at ≥ 50 mg/kg/day. These reversible changes were considered adaptive response to increased metabolism (increased hepatic glucuronosyltransferases (ugt1a1, 1a6, 2b1), which are responsible for metabolism of thyroid hormones) and excretion of thyroid hormones and not considered significant test article related adverse effects. Follicular adenomas were observed in two males at 100 mg/kg/day, three males, and one female at 250 mg/kg/day. These lesions were partially resolved in the recovery period. Testes: No effect on testes was reported. Minor observations in 1 or 2 animals at 10 mg/kg/day and at 250 mg/kg/day were considered sporadic due to lack of any dose responsiveness.

[Other evaluations] n/a

Source: Pharmacology/toxicology reviewer generated table base on Study Report 8310210
Abbreviations: Hb, hemoglobin; n/a, not applicable; PCV, packed cell volume; RBC, red blood cells

To further evaluate the occurrence of thyroidal follicular hyperplasia and adenomas in this 26-week rat study, a supplemental 26-week study (T-16.021) was performed with a detailed thyroid functional and histopathological evaluation in male Wistar and SD rats. This study is reviewed below.

Study Number/Title: T-16.021/ACT-132577E – 26-Week Toxicity Study by the Oral Route (Gavage) in the Male Rat Followed by a 9-Week Treatment-Free Period

Key Study Finding

Adverse histopathology findings:

- A dose-dependent increase in centrilobular hepatocellular hypertrophy accompanied by increased centrilobular hepatocellular fatty change was observed in liver. At 250 mg/kg/day a moderate hepatocellular vacuolar degeneration/necrosis of hypertrophic hepatocytes was observed.
- Reversible increases in thyroid-stimulating hormone were noted in Wistar rats (250 mg/kg/day) and SD rats (all the dose levels tested), establishing the cause of thyroid follicular cell hyperplasia and adenomas observed in the original 26-week rat study.

- Reversible findings in the thyroid gland included a dose-dependent minimal to slight follicular cell hypertrophy with correlating enlarged thyroid and increased weight at ≥ 50 mg/kg/day and minimal or slight focal follicular cell hyperplasia in two SD rats treated with 250 mg/kg/day. No follicular adenomas were observed in this study.
- Minimal dilation of seminiferous tubules (50 or 250 mg/kg/day) and increased incidence of tubular degeneration/atrophy was observed in testes at 250 mg/kg/day which were resolved completely at the end of recovery.
- The NOAEL was determined to be 50 mg/kg/day, based on liver necrosis and testicular tubular degeneration/atrophy observed at 250 mg/kg/day. The NOAEL exposures represented AUC_{0-last} values of 554 h* μ g/mL in Wistar rats and 474 h* μ g/mL in SD rats, or approximately 16 and 14-fold the AUC at MRHD, respectively.

Table 56. Study Information for Study Number T-16.021/ACT-132577E

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 10, 50 and 250 mg/kg and once daily
Route of administration (volume)	Oral gavage (10 mL/kg/day). Oral route is the route of administration in humans.
Formulation/vehicle	Aqueous solution of 0.5% methylcellulose containing 0.5% Tween 80, in water
Species/strain	• Strain 1: rat Wistar: Crl: WI (Han). • Strain 2: rat Sprague Dawley Crl: SD. Above two strains were used in this study to further characterize the thyroid findings noted in the 26-week rat study (8310210) as they were observed in the preliminary 2-week study (T-16.020).
Number/sex/group	20 (main study) and 5 (recovery) and 9 (toxicokinetic)/male/strain/group
Age	7 weeks (main animals). 8 weeks (satellite animals).
Satellite groups/unique design	9 (control/treated)/sex/group
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer generated table base on study report T-16.021.
Abbreviation: GLP, good laboratory practices

Table 57. Observations and Results for Study Number T-16.021/ACT-132577E

Parameters	Major Findings
Mortality	In the Wistar rats' group, five animals were either found dead (control (n=1) on Day 154, 10 mg/kg/day (n=1) on Day 151, and 50 mg/kg/day (n=1) on Day 149) or sacrificed early due to moribund condition (50 mg/kg/day (n=2) on Day 95 and 179). In the SD rats' group, four animals were either found dead (control (n=1) on Day 74) or sacrificed early due to moribund condition (control (n=1) on Day 171 and 250 mg/kg/day (n=1) on Day 134). The cause of death was identified as misintubation for the animals that were found dead and the animals that were found moribund were not identified as treatment-related. Therefore, it was unlikely that these early deaths could be attributed to the treatment with test article.

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Parameters	Major Findings
Clinical signs	Minor findings in the treatment groups were not considered adverse effects.
Body weights	Decrease in mean body weight was observed in both of the species (-12% in Wistar rats and -11% in SD rats from Day 182 compared to respective control values) at 250 mg/kg/day and less pronounced during the recovery phase.
Ophthalmoscopy	Incidental findings were not considered treatment-related.
Hematology	No treatment related changes were observed except a slight reduction in RBC, Hb and PCV (-7% maximum)
Clinical chemistry	Increases in total protein with associated increases in globulin levels were observed in Wistar and SD rats at 250 mg/kg/day. Lower triglyceride levels (-74% in Wistar rats and -52% in SD rats at Week 13 and -65% in Wistar rats and -62% in SD rats at Week 26) were noted at 250 mg/kg/day. These changes were reversible at the 9-week recovery phase.
Urinalysis	No effects on urine parameters observed
Thyroid hormone	Reversible higher levels of thyroid hormone (TSH) were noted in Wistar rats (250 mg/kg/day) and SD rats (all the dose levels tested).
Gross pathology	Enlarged liver (≥ 50 mg/kg/day in Wistar rats and ≥ 10 mg/kg/day in SD rats) was observed. Enlarged thyroid glands were observed at 250 mg/kg/day in both Wistar rats and SD rats.
Organ weights	Reversible dose-dependent increase in liver weight was observed in both strains. Thyroid gland weight was increased ≥ 50 mg/kg/day.
Histopathology Adequate battery: Yes	Liver: In both strains a dose-dependent centrilobular hepatocellular hypertrophy accompanied by increased centrilobular fatty change was observed in all the treated animal groups. A moderate hepatocellular vacuolar degeneration/necrosis in the hypertrophic hepatocytes (several animals at 250 mg/kg/day) with minimal multinucleated hepatocytes in five animals was observed. These findings were either fully (hepatocellular degeneration/necrosis and multinucleated hepatocytes) or partially (hepatocellular hypertrophy and fatty changes) reversed at the end of the recovery phase. Thyroid glands: A dose-dependent follicular cell hypertrophy was recorded at minimal and/or slight severity degree of all treated groups which is accompanied by minimal or slight focal follicular cell hyperplasia in two SD rats treated with 250 mg/kg/day. These findings were fully reversed at the end of the recovery phase. Testes: Minimal dilation of seminiferous tubules of the testes of both strains was observed at 50 or 250 mg/kg/day, and an increased incidence of tubular degeneration/atrophy at 250 mg/kg/day. Both findings showed complete reversibility after the recovery period. There was no finding of the testes reported in another 26-week rat study at the same dose levels. The dilation of seminiferous tubules only observed at the 50 mg/kg/day was of minimal severity and low incidence, hence, was not considered adverse.
[Other evaluations]	n/a

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-16.021

Abbreviations: Hb, hemoglobin; n, number; n/a, not applicable; PCV, packed cell volume; RBC, red blood cells; SD, Sprague-Dawley; TSH, thyroid stimulating hormone

In addition to the above listed chronic toxicity studies, multiple short-term or subchronic studies were conducted in rats.

13.1.3.1.2. Repeat Dose Toxicity Studies in Dogs

Repeat dose toxicity studies were conducted in dogs for up to 39 weeks with oral dose levels from 5 to 1000 mg/kg/day. Key findings are summarized below.

39-Week (13-Week Recovery) Toxicology Study

Study Number/Title: T-15.053/ACT-132577: 39 Week Oral (Capsule) Administration Toxicity Study in the Dog Followed by a 13 Week Treatment-Free Period

Key Study Findings

- Dose related occurrence of noisy respiration was observed at ≥ 25 mg/kg/day.
- Clinical signs, including hunched posture, pale or thin appearance, and subdued/sluggish behavior were observed at the high dose (75 mg/kg/day), leading to its reduction to 50 mg/kg/day starting from Day 163 in males and Day 165 in females.
- Testes: minimal to slight tubular degeneration at doses ≥ 25 mg/kg/day.
- Enlarged liver lobes and/or mottled livers were observed (males at 25 mg/kg/day and both sexes at 75/50 mg/kg/day) with associated increased weights and hepatocellular hypertrophy at ≥ 25 mg/kg/day. These changes were fully resolved at the end of recovery.
- The NOAEL was determined at 5 mg/kg/day, based on noisy respiration, tubular degeneration in the testes at higher doses. The NOAEL was associated with AUC_{0-24hr} values of $374 \text{ h} \cdot \mu\text{g/mL}$, approximately 11-fold the exposure at MRHD.

Table 58. Study Information for Study Number T-15.053/ACT-132577

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 5, 25, 75/50 (50 mg/kg was from Day 165 and 163 for male and females, respectively) and once daily
Route of administration	Oral gavage (capsule)
Formulation/vehicle	Empty gelatin capsule
Species/strain	Beagle dogs
Number/sex/group	4 (main) or 3 (recovery) /sex/group
Age/weight	40 to 45 weeks/7.73 to 12.60 kg
Satellite groups/unique design	None
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-15.053
Abbreviation: GLP, good laboratory practices

Table 59. Observations and Results for Study Number T-15.053/ACT-132577

Parameters	Major Findings
Mortality	No mortality
Clinical signs	Noisy respiration (≥ 25 mg/kg/day) apparent from Day 30. Minimal to moderate subdued/sluggish behavior and hunched posture was noted from Day 54 at 75/50 mg/kg/day.
Body weights	Body weight gain was lower for both sexes administered ≥ 25 mg/kg/day. Lower body weight gain was (17% in males or 90% in female) observed in 25 mg/kg/day group (Days 1 to 274). The body

Parameters	Major Findings
	weight gain was 61% or 72% lower in males or females in 75 mg/kg/day group (Days 1 to 274) and comparable between Days 162 and 274.
Feed consumption	Apparent decreased intake was observed in the first few weeks of the dosing phase at 75/50 mg/kg/day. Moistened diet/supplements were provided as required.
Ophthalmoscopy	No treatment-related effect was observed
Hemodynamics and ECG measurements	No treatment-related effect on ECG or hemodynamic parameters was noted.
Hematology	At 75/50 mg/kg/day reduction in the RBC count, hemoglobin, and PCV (hematocrit) and red cell distribution width was noted in females (at all time points) and reduction in Hb and RBC count was noted in males (at Day 268).
Clinical chemistry	Sporadic increase in AST and ALT activities were observed in a few animals (75/50 mg/kg/day). Low urea levels were noted at 75/50 mg/kg/day. These effects were reversed during the recovery phase.
Urinalysis	No treatment related effect was observed
Gross pathology	Enlarged liver lobes and/or mottled livers were observed (males at 25 mg/kg/day and both sexes at 75/50 mg/kg/day) with associated increased incidences of hepatocellular hypertrophy.
Organ weights	Liver weights, absolute and relative (organ/brain and organ/body weights) were slightly increased at ≥ 25 mg/kg/day and reversed at the end of recovery period.
Histopathology Adequate battery: Yes	<u>Liver:</u> Reversible increases in the incidence of hepatocellular hypertrophy were noted in both sexes (≥ 25 mg/kg/day). Nasal cavity: Congestion increased in incidence and/or severity (≥ 25 mg/kg/day) was associated with minimal to moderate submucosal edema, goblet cell proliferation (syn. Hyperplasia). Single incidences of a minimal hyperchondrosis and hyperostosis at all dose levels and submucosal deposition of loose connective tissue in a few animals (75/50 mg/kg/day) were observed. <u>Testes:</u> Minimal to slight tubular dilation was observed at all doses but minimal to slight tubular degeneration was only observed at ≥ 25 mg/kg/day. One animal at 75/50 mg/kg/day was observed with hypoplasia of the germinal epithelium. Fibrous tissue replacing was observed in all testicular tissues, which was associated with aspermic and hypoplastic epididymides. Peri-/arteritis in the testes and the epididymides was observed. The fibrosis was considered as a consequence of the spontaneous peri-/arteritis which may be leading to testicular atrophy. <u>Heart:</u> Minimal chronic, fibrosing myocardial and pericardial inflammation with hemosiderin deposition was observed in one animal at 25 mg/kg/day.
Other evaluations	n/a

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Source: Pharmacology/toxicology reviewer generated table base on Study Report T-15.053
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ECG, electrocardiogram; Hb, hemoglobin; n, number; n/a, not applicable; PCV, packed cell volume; RBC, red blood cells

In addition to the above listed chronic toxicity studies, multiple subchronic studies were conducted in dogs.

13.1.3.2. Genotoxicity Studies

Aprocitentan showed no mutagenic or clastogenic activity in a standard battery of genotoxicity studies, which includes a bacterial reverse mutation study, an in vitro chromosomal aberration study in human lymphocytes, and an in vivo micronucleus study in rats.

Table 60. Genetic Toxicology

Study/Study Number	Key Study Findings
Study no: T-14.025 Study title: ACT-132577: Salmonella typhimurium Reverse-Mutation Assay Doses tested: 3, 10, 33, 100, 333, 1000, 2500, 5000 µg/plate for <i>Salmonella</i> strains TA 1535, TA 1537, TA 98, TA 100, and TA 102 GLP compliance: Yes Study is valid: Yes	Aprocitentan did not increase the number of revertants in any of the strains tested in the presence or absence of metabolic activation; therefore, aprocitentan was considered negative for mutagenicity in this bacterial reverse mutation assay. Positive controls demonstrated expected S9- and strain-dependent increases in revertant colonies.
Study no: T-14.026 Study title: Evaluation of the Ability of ACT-132577 to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes Doses tested: Experiment 1: Up to 500 µg/mL for a 3 h exposure time with a 24 h fixation time in the absence and presence of S9 mix Experiment 2: Up to 75 µg/mL for a 24 h continuous exposure time with a 24 h fixation time in the absence of S9 mix GLP compliance: Yes Study is valid: Yes	Aprocitentan did not induce any increase in the number of cells with chromosome aberrations and did not have an effect on the number of polyploid cells or cells with endoreduplicated chromosomes in the absence and presence of S9 mix. Positive control chemicals induced a statistically significant increase in the incidence of cells with chromosome aberrations. Aprocitentan is not considered clastogenic in human lymphocytes.

Study/Study Number	Key Study Findings
Study No: T-15.006 Study Title: ACT-132577E: Rat Bone Marrow Micronucleus Assay Species/strain: Rat/Han Wistar Number/sex/group: 6/sex/group Doses tested: 100, 500 and 1400 mg/kg/day Route and duration: Oral, daily on Day 1 and Day 2 GLP compliance: Yes	No mortality, drug related clinical signs or effect on body weights were observed. Animals were systemically exposed to ACT-132577E. Male animals showed significant heterogeneity in MN-PCE frequencies at ≥ 500 mg/kg/day. One animal had shown to have a MN-PCE frequency that exceeded the laboratory's historical control ranges in 1400 mg/kg/day and led to nonsignificant increase in the group mean frequency of MN-PCE. Two female animals (one each at 100 and 500 mg/kg/day) frequencies of MN-PCE were that exceeded the laboratory's historical control ranges. No significant increase in the group mean frequency of MN-PCE were observed. Overall, ACT-132577E treatment did not alter %PCE and MN-PCE frequencies; therefore, it is considered not induce micronuclei in the polychromatic erythrocytes of the bone marrow.

Source: Pharmacology/toxicology reviewer generated table base on Study Reports T-14.025, T-14.026, and T-15.006
Abbreviations: GLP, good laboratory practices, h, hour; MN-PCE, micronucleated polychromatic erythrocyte, no., number; PCE, polychromatic erythrocyte; S9, supernatant at 9000 g; TA, Tester strain (Ames test)

13.1.3.3. Carcinogenicity Studies

No dedicated carcinogenicity studies were conducted with aprocitentan. Aprocitentan is a major metabolite of macitentan, and its exposure represented $\geq 38\%$ of the total exposure to macitentan and aprocitentan in the macitentan carcinogenicity studies. Therefore, the macitentan carcinogenicity studies, conducted in B6C3F1 mice and Wistar rats, were considered acceptable to assess the carcinogenic potential of aprocitentan. The studies in mice and rats were conducted in accordance with good laboratory practice (GLP) regulations and prior concurrence with the CDER's Executive Carcinogenicity Assessment Committee (CAC) was obtained regarding the strain, number of animals employed, and doses evaluated. Both studies were reviewed previously in NDA 204410 and were concluded to be negative, as described in the label of macitentan. Below is a brief summary of the results of those studies based on previous review.

13.1.3.3.1. T-09.160: ACT-064992: 104-Week Oncogenicity (Gavage) Study in the B6C3F1 Mouse

Male and female B6C3F1 mice (60 mice/sex/group for main study and 24 mice/sex/group for toxicokinetic evaluation) were treated with macitentan (vehicle; 0.5% methylcellulose in purified water, 5, 30, 100, and 400 mg/kg/day, oral) for a duration of 104 weeks, except for females of the 400 mg/kg dose group. Due to high morbidity/mortality in females (35/60), the 400 mg/kg/day group was led to early termination at Week 79. The cause of death could not be established in most animals.

Clinical signs of respiratory distress (e.g., breathing noises, labored breathing, tachypnea, and cyanosis) were observed in males at 400 mg/kg/day and in females at ≥ 100 mg/kg/day from Week 33 onwards. Dose-related decrease in body weights was observed in males (-4%, -7%,

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and -17% final body weights at 30, 100, and 400 mg/kg/day, respectively) and in females (-8% and -19% final body weights at 30 and 100 mg/kg/day, respectively) mice.

In histological evaluation, treatment-related proliferation of the nasal mucosa and submucosal glands was observed with associated increased incidence of inflammatory infiltration in the submucosa / submucosal glands. Hyaline inclusions and increased secretion were observed at doses $\geq$ 100 mg/kg/day, which could be the reason for the respiratory distress noticed in this study. The incidence of hepatocellular hypertrophy was increased in males at all dose levels. Mean severity and incidence of endometrial cysts in the uterus was increased in females at 100 mg/kg/day, which was associated with increase in uterus organ weight.

In this study macitentan (ACT-064992) did not increase the incidence of neoplastic lesions when tested up to 400 mg/kg/day in male mice and 100 mg/kg/day in female mice, which is a maximum tolerated dose (MTD) in males and females, respectively. The aprocitentan exposure (AUC) at macitentan dose of 100 mg/kg/day in Week 26 provided approximately 34-fold (females) and 50-fold (males) human exposure at the MRHD of aprocitentan (12.5 mg).

Executive Carcinogenicity Assessment Committee Conclusions

- The Committee found that the study was acceptable, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

13.1.3.3.2. T-09.159: ACT-064992: 104-Week Oncogenicity (Gavage) Study in the Wistar Rat

Male and female rats (Wistar, 51 rats/sex/group) were treated with macitentan (vehicle; 0.5% methylcellulose in purified water, 10, 50 and 250 mg/kg/day, oral) for a duration of 104 weeks, except for female rats of the 50 and 250 mg/kg dose group. In the female rats, due to clinical signs at doses $\geq$ 50 mg/kg/day and mortality at 250 mg/kg/day, the mid and high dose groups were suspended in weeks 50 and 51 and resumed in week 52 at doses 25 and 50 mg/kg/day.

Body weight was decreased in males at 250 mg/kg/day and females at 50/25 and 250/50 mg/kg/day. Respiratory distress (breathing noises, labored breathing, tachypnea, and cyanosis) was observed in a dose-dependent manner at all doses tested with higher incidences in the females.

In this study, macitentan (ACT-064992) treatment did not increase the incidence of neoplastic lesions when tested up to an MTD. The aprocitentan exposure (AUC) at macitentan dose of 50 mg/kg/day dose in Week 26, provided approximately 8-fold (male) and 14-fold (females) the human AUC at the MRHD for aprocitentan.

Executive Carcinogenicity Assessment Committee Conclusions

- The Committee found that the study was acceptable, noting prior Executive CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

13.1.3.4. Reproductive and Developmental Toxicity

The Applicant submitted a fertility and early embryonic development study (Segment I) with aprocitentan alone and referred to NDA 204410 (Opsumit) for embryo-fetal development (EFD) studies (Segment II) and pre- and postnatal developmental (PPND) study with macitentan. This was acceptable because aprocitentan represented $\geq 50\%$ of the combined exposure to macitentan and aprocitentan in rats and rabbits, and the plan was agreed upon with the FDA prior to NDA submission. The referenced EFD and PPND studies were reviewed previously under NDA 204410.

During the NDA review cycle, the Applicant submitted additional EFD studies with aprocitentan alone to support their proposed (b) (4) REMS. While the Agency was not obligated to accept those data for review during the NDA review cycle, the data were nonetheless reviewed. The adequacy of the submitted information to address Agency concerns for embryo-fetal risk is discussed in Section 13.2.1. The general conclusion was that the data (b) (4) compared to the other members of the endothelin receptor antagonist (ERA) class, all of which demonstrate teratogenicity at clinically relevant exposures in rats due to a shared mechanism of action.

13.1.3.4.1. Fertility and Early Embryonic Development

Study Number/Title: T-16-001/ACT-132577E – Fertility Toxicity Study by the Oral Route (Gavage) in the Male Rat (Segment I)

Key Study Findings

- No aprocitentan-related effects on male gonadal function, mating behavior or virility were observed based on reproductive indices and sperm parameters.
- Minimal dilation of the seminiferous tubules in the testes was observed in 1/22 rats at dose of 50 mg/kg/day and 4/22 rats at dose of 250 mg/kg/day.
- Dose-dependent enlarged liver and increased liver weight with associated centrilobular hepatocellular hypertrophy was observed with increasing severity. Hepatocellular vacuolar degeneration/necrosis (minimal to slight) of hypertrophic hepatocytes was observed at 250 mg/kg/day. A resultant dose-dependent minimal and/or slight follicular cell hypertrophy in the thyroid glands was observed, which represents a rat-specific response to increased turnover of thyroid hormone in the liver.
- The no observed effect level for male fertility was 250 mg/kg/day, based on lack of effect on gonadal function, mating behavior and reproductive performance. The NOAEL for general toxicity was determined at 50 mg/kg/day, based on hepatocellular vacuolar degeneration/necrosis at 250 mg/kg/day, which was associated with AUC_{0-24h} values of 468 µg.hr/mL in male rats, approximately 13-fold the AUC at the MRHD.

GLP Compliance: Yes

Table 61. Methods of Fertility and Early Embryonic Development Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0, 10, 50, and 250 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose containing 0.5% Tween 80, in water
Species/strain	Wistar rat: CrI: WI (Han)
Number/sex/group	22 per sex/group
Satellite groups	6 males for toxicokinetics evaluation
Study design	Animals were treated during a 10-week pre-mating period, throughout mating, and up to 3 weeks after mating.
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-16-001

Table 62. Observations and Results of Fertility and Early Embryonic Development Study in Rats

Parameters	Major Findings
Mortality	No test article-related mortality. Two males (one in 250 mg/kg/day and one in 50 mg/kg/day) were euthanized early for nontreatment related morbidity.
Clinical signs	No adverse effects were observed
Body weights	No adverse effects were observed
Mating performance and fertility	No effect on fertility was observed
Sperm analysis	No test article related effect on testicular sperm count, on the epididymal sperm count, on motility or morphology parameters was observed.
Caesarean	Pre-implantation data (mean numbers of corpora lutea, implantation sites and the percentage pre-implantation loss) was not affected in females mated with the treated males. Similarly, no effect on postimplantation data (mean live litter size) was noted.
Organ weights	No differences in mean body, testis, or epididymis weights were noted. Dose-related increases in liver (all groups), thymus (≥ 50 mg/kg/day) and thyroid (250 mg/kg/day) weights were noted.
Macroscopic observations	Paternal observations: Enlarged liver (one male at 50 mg/kg/day and four males at 250 mg/kg/day) was observed.
Necropsy findings	Liver: Dose-dependent increase in number and severity of centrilobular hepatocellular hypertrophy along with increased centrilobular fatty changes (incidence and mean severity; 1/1.0, 10/1.1, 22/1.6 and 22/3.0 in control and 10, 50, and 250 mg/kg/day, respectively) with three males with hepatocellular degeneration/necrosis (0 vs. 3/1.3 in control vs. 250 mg/kg/day). Increased centrilobular fatty changes was noted (5/1.0, 11/1.2, 8/1.4 and 9/1.4 in control and 10, 50, and 250 mg/kg/day, respectively). Thyroid glands: Dose-dependant follicular cell hypertrophy (minimal and/or slight) was observed in males (0, 6/1.0, 21/1.1 and 22/1.5 in control and 10, 50, and 250 mg/kg/day, respectively). Testes: Five males (one in 50 mg/kg/day and four in 250 mg/kg/day) observed with minimal dilation of seminiferous tubules.
Cesarean section data	

Source: Pharmacology/toxicology reviewer-generated table base on Study Report T-16-001

Abbreviation: vs., versus

Study Number/Title: T-16.002/ACT-132577E – Fertility Toxicity Study by the Oral Route (Gavage) in the Female Rat (Segment I)

Key Study Findings

- No aprocitentan-related effect on female mating performance was observed.
- The mean estrous cycle length was slightly increased, and a higher percentage of acyclic females was observed at 250 mg/kg/day.
- Mean number of corpora lutea and implantation sites were significantly lower (≥ 50 mg/kg/day) compared to control.
- The NOAEL was 10 mg/kg/day, based on the effect on early gestation (pre-implantation loss), which was associated with AUC_{0-24h} values of 158 $\mu\text{g}\cdot\text{hr}/\text{mL}$ in females, approximately 5-fold the AUC at the MRHD.

GLP Compliance: Yes

Table 63. Methods of Fertility and Early Embryonic Development Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 10, 50, and 250 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose containing 0.5% Tween 80, in water
Species/strain:	Wistar rat: Crl: WI (Han)
Number/sex/group:	22 per sex/group
Satellite groups:	6 females for toxicokinetic evaluation
Study design:	Animals were treated two weeks prior to pairing, during pairing with untreated virgin males and until Day 7 of gestation.
Deviation from study protocol affecting interpretation of results:	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table base on study report T-16.002

Table 64. Observations and Results of Fertility and Early Embryonic Development Study in Rats

Parameters	Major Findings
Mortality	No test article related mortality occurred. One female (250 mg/kg/day) was removed on Day 29 due to its poor health. The animal was found to be pregnant at necropsy with sore/crust on the skin on the abdomen and treatment-related slight centrilobular hepatocyte hypertrophy in the liver.
Clinical signs	No treatment related adverse effect was observed.
Body weights	No treatment related adverse effect was observed. Slightly lower body weight (GD Day 0-13) and mean terminal body weight (-4%) was observed.
Estrous cycle	Higher percentage (9% vs. 23% in control vs. 250 mg/kg/day) of being acyclic or with acyclic period with an increased mean estrus cycle length (4.1 vs. 4.5 days in control vs. 250 mg/kg/day) was observed.
Mating performance and fertility	No effect on mating performance was observed.
Gravid uterus weight	Slightly lower than the control and consistent with the smaller litter size

Parameters	Major Findings
Caesarean	Pre-implantation data: Mean number of corpora lutea was significantly lower at 250 mg/kg/day (14, 13.9, 13.2 and 12 in control, 10, 50 and 250 mg/kg/day, respectively). Mean number of implantation sites was significantly less at ≥ 50 mg/kg/day (13.1, 13.4, 10.9 and 10.8 in control, 10, 50 and 250 mg/kg/day, respectively). Post-implantation data: Not affected by the treatment.
Organ weights	No significant effect on ovary weights observed
Macroscopic observations	Maternal observations: No adverse findings observed
Necropsy findings	No histopathology studies were performed for the reproductive organs.
Cesarean section data	

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-16.002

Abbreviations: GD, gestational day; vs., versus

13.1.3.4.2. Embryo-Fetal Development

EFD studies were cross-referenced from the NDA 204410 for Opsumit (macitentan) and the results are summarized below. Aprocitentan is an active and the major metabolite of macitentan. Its exposure in rats and rabbits represented $\geq 50\%$ of total exposure with administration of macitentan.

Rat Embryofetal Development Toxicity Study

A preliminary embryo-fetal toxicity study (Study # T-05.008) was conducted in Wistar rats for the purpose of dose selection in the main embryo-fetal toxicity studies. Administration of macitentan (0, 150, 450 and 1500 mg/kg/day) from Day 6 to Day 17 of the gestation period resulted maternal toxicity at 1500 mg/kg/day and embryo-fetal toxicity at all doses tested. Therefore, 150 mg/kg/day was selected as the highest dose in the main study. Below are the definitive study results.

Study Number/Title: T-12.804/ACT-132577E: ACT-064992: Oral (Gavage) Embryo-Fetal Development Study in the Rat With Toxicokinetic Sampling

Key Study Findings

- Fetal abnormalities, defects in the head/neck, heart vessels and skeletal (skull), were observed at all the doses tested.
- Macitentan treatment was teratogenic in rats starting at the lowest dose tested (3 mg/kg/day), which corresponds to an $AUC_{0-24\text{ h}}$ of $36.8 \mu\text{g}\cdot\text{hr}/\text{mL}$ of aprocitentan. This is approximately equivalent to the exposure at MRHD for aprocitentan based on AUC.

GLP Compliance: Yes

Table 65. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing	0, 3, 10 and 150 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose (in water for injection).
Species/strain	CrI:WI(Han)

Parameter	Method Details
Number/sex/group	20 per sex/group
Satellite groups	2 (control) to 3 (treatment) females/group TK
Study design	Dams treated once daily from GD 6-17. TK blood sampling was performed on gestation Days 6 and 17.
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-12.804

Abbreviations: GD, gestational day; TK, toxicokinetic

Table 66. Observations and Results of Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	No mortality was observed.
Clinical signs	No treatment-related adverse clinical signs were noted.
Body weights	Mean body weight loss was observed at 150 mg/kg/day
Necropsy findings	Macroscopic findings: No treatment-related adverse effects were observed.
Cesarean section data	Ovarian and uterine examination and litter observations: Mean fetal body weights were lower than the control at 150 mg/kg/day. Fetal abnormalities were noted at all the doses tested.
Necropsy findings	Fetal abnormalities were noted at all the doses tested, which include defects in the head/neck, heart vessels and skeletal (skull).
Offspring	
Toxicokinetics	Exposure of Macitentan (ACT-064992) and Aprocitentan (ACT-132557)

Dose level (mg/kg/day)	ACT-064992			ACT-132557		
	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)
Day 6 of gestation						
3	6	2050	31400	10	1490	28300
10	6	5140	80500	10	2850	51700
150	6	39100	548000	10	28100	479000
Day 17 of gestation						
3	4	2140	26500	6	1960	36800
10	4	6900	89500	6	4560	88600
150	4	34200	431000	6	33600	529000

Source: Applicant-generated table from study report T-12.804.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-12.804

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours; C_{max}, maximum concentration; T_{max}, time-to-peak concentration

Rabbit Embryofetal Development Toxicity Study

A preliminary embryo-fetal toxicity study was conducted in rabbits. Administration of macitentan (0, 2.5, 5, 12.5 and 25 mg/kg/day) from Day 6 to Day 19 of the gestation period did not result in maternal toxicity but embryo-fetal toxicity was observed at all the doses tested.

Below are the definitive study results.

Study Number/Title: T-05.029/ACT-064992 – Preliminary Embryo-Fetal Toxicity Study by Oral Gavage Administration to Rabbits ((b) (4))

Key Study Findings

- Fetal abnormalities, mandibular arch and cardiovascular abnormalities and minor skeletal and visceral abnormalities, were observed at all the dose levels tested.

- Teratogenicity was observed in rabbits starting at the lowest macitentan dose (2.5 mg/kg/day) tested, which corresponds to an AUC_{0-24 h} of 520 µg*hr/mL for aprocitentan, approximately 15-fold the exposure at MRHD of aprocitentan.
- No maternal toxicity was observed in dams at macitentan doses up to 25 mg/kg/day.

GLP Compliance: Yes

Table 67. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing	0, 2.5, 5, 12.5 and 25 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose (in water for injection).
Species/strain	Rabbit/New Zealand white
Number/sex/group	8 per sex/group
Satellite groups	No satellite group included
Study design	Dams treated once daily from GD 6-19. TK blood sampling was performed on gestation Days 6 and 19.
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-05.029

Abbreviations: GD, gestational day; TK, toxicokinetic

Table 68. Observations and Results of Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	No mortalities were reported
Clinical signs	No treatment-related adverse clinical signs were noted.
Body weights	Maternal bodyweight gain is retarded at 25 mg/kg/day
Necropsy findings	Macroscopic findings: No treatment related adverse observations.
Cesarean section data	Ovarian and uterine examination and litter observations: High incidence of postimplantation loss was noted at 25 mg/kg/day. Litter size and weight was lower at 25 mg/kg/day.
Necropsy findings Offspring	Fetal mandibular arch and cardiovascular abnormalities and minor skeletal and visceral abnormalities were reported at all the dose levels tested.

Toxicokinetics

Plasma Exposure of ACT-064992 (Macitentan)

Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)	
	Day 6	Day 19	Day 6	Day 19
2.5	7.54	7.95	114	118
12.5	31.8	22.2	543	323
25	44.5	29.1	724	396

Source: Applicant-generated table from study report T-05.029.

Plasma Exposure of ACT-132577 (Aprocitentan)

Dose level (mg/kg/day)	C _{max} (µg/mL)		AUC ₂₄ (µg.h/mL)	
	Day 6	Day 19	Day 6	Day 19
2.5	6.04	23.7	101	520
12.5	37.5	107	525	2280
25	72.1	206	982	4290

Source: Applicant-generated table from study report T-05.029.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-05.029

Abbreviations: AUC₂₄, area under the concentration-time curve at 24 hours; C_{max}, maximum concentration

13.1.3.4.3. Rat Pre- and Postnatal Development Study

Study Number/Title: T-09.617/ACT-064992: Study for Effects on Pre- and Postnatal Development Including Maternal Function in the Wistar Rat

The PPND study was cross-referenced from the macitentan application, NDA 204410, Opsumit, and the results are summarized below.

Key Study Findings

F0 Dams

- Postnatal loss was increased at all dose levels resulting in decreased birth and viability indices.
- Prewaning loss was increased with corresponding decrease in weaning index at 250 mg/kg/day.
- Several pups were found dead during the first litter check after weaning and “no milk in the stomach” was observed in several pups during the lactation period.

F1 Pups

- Mean bodyweight and body weight gain were reduced on Day 21 and remained reduced on Day 42.
- Balano-preputial separation and opening of vagina were delayed at 250 mg/kg/day.
- At necropsy the following effects were observed.
 - Liver-enlarged hepatocytes at periportal region, bile duct hyperplasia and inflammatory foci in the liver.
 - Male reproductive organs – reduced size of testes and epididymides with correlated reduced organ weights in some F1 pups at all treated dose levels; increased incidence of minimal/slight tubular atrophy in F1 males at dam dose of 250 mg/kg/day.

F1 Generation

- Number of female animals that did not mate or were not pregnant increased.
- Preimplantation loss increased with reduced number of implantation sites and reduced mean number of liver embryos at termination.
- Liver size was reduced with thickened or thickened/enlarged lobes. Hepatocytes were increased in size at periportal location, bile duct hyperplasia and some inflammatory foci were observed in some animals of all treated groups.
- Testes, epididymides and seminal vesicles reduced in size with correlated reduction in organ weights. Increased incidence of minimal/slight tubular atrophy was noticed at 250 mg/kg/day.

NDA 217686
 TRYVIO (aprocitentan)

No NOAEL was determined for reproduction parameters for F0 dams or F1-pups, based on adverse findings at all doses tested.

Macitentan treatment exhibited adverse effects in rats starting at the lowest dose of 10 mg/kg/day, which corresponds to aprocitentan AUC_{0-24 h} of 69.8 µg*hr/mL, approximately 2-fold the exposure at the MRHD of aprocitentan.

GLP Compliance: Yes

Table 69. Methods of Oral PPND Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0, 10, 50 and 250 mg/kg/day
Route of administration	Oral gavage
Formulation/vehicle	0.5% (w/v) methylcellulose in Milli-Q-Water
Species/strain	Rat, RccHanTM: WIST(SPF)
Number/sex/group	24 females/group 22 F1 offspring/group
Satellite groups	4 males/group
Study design	Dams treated once/day from Day 17 postcoitum until Day 20 postpartum. Day 17 postcoitum was chosen due to known teratogenicity. Pups were not treated.
Deviation from study protocol affecting interpretation of results	Deviations were not considered to have affected the outcome of the study objectives.

Source: Pharmacology/toxicology reviewer-generated table based on study report T-09.617

Abbreviations: F1, first generation of offspring or first filial generation; PPND, pre- and postnatal development, w/v, weight by volume

Table 70. Observations and Results of PPND Study in Rats

Parameters	Major Findings
Mortality	No mortality was observed in F0 female rats.
Clinical signs	No treatment-related adverse clinical signs were noted.
Body weights/food consumption	F0 dams: No effect on body weights or body weight gain was observed No dose dependent increases (Days 19 to 18 postpartum) observed in mean body weight at 10 and 50 mg/kg was not considered treatment-related. Food consumption was significantly decreased at 250 mg/kg/day. F1 pups: Mean body weight gain and body weights were reduced on Day 21 postpartum and remained reduced on Day 42.
Necropsy findings Cesarean section data	No effect on gestation duration was observed. Postimplantation loss was slightly increased at all dose levels and significant at 250 mg/kg/day. Reduction in living pups and reduced birth index (significant at 250 mg/kg/day) was observed. Increased postnatal loss resulted in decrease in viability index (96.8%, 96.3%, and 94.3% in 10, 50, and 250 mg/kg dose compared to 99.6% in control). Significant increase in preweaning loss (between Days 5 and 21 postpartum) was observed at 250 mg/kg/day.
Clinical observations Offspring	Dose-related increase in pups without milk in the stomach and dead or missing pups were observed. Slight but statistically significant delay in balano-preputial separation (27.0 days compared to 26.1 days in the control group) and opening of vagina (34.5 days compared to 32.9 days in the control group) were observed at 250 mg/kg/day. No effect on locomotor activity, learning and memory was observed.

Parameters	Major Findings
Body weights/food consumption Offspring	Pups' body weight was decreased from Day 1 postpartum and stayed reduced at 250 mg/kg/day.
Reproductive performance of offspring	Male animal body weight and body weight gain were significantly lower in all dose groups during preparing until the end of the after-pairing period. Increase in number of F1 males/females that were not mated or were not pregnant resulted in a dose-dependent decrease in fertility index. Pre-implantation loss was increased with correlating reduced number of implantation sites and mean number of live embryos at termination.
Necropsy findings Offspring	Liver: In the macroscopical observations F1 pups' liver appeared reduced in size, thickened, or thickened with enlarged lobes at all dose levels. In microscopic examination of F1-generation animals, hepatocytes of the periportal zone appeared enlarged and bile duct hyperplasia and inflammatory foci was observed at all dose levels. Testes: The reduced size of testes and epididymides with correlated reduced organ weights was observed in some animals in all treated F1 pups. Increase incidence of minimal/slight testicular tubular atrophy was observed in F1 males at 250 mg/kg/day.

Toxicokinetics

Toxicokinetics of PPND Study in Rats

Macitentan Dose (mg/kg/day)	Time	Macitentan	ACT-132577	ACT-373898
		AUC ₀₋₂₄ (µg·h/mL) Female	AUC ₀₋₂₄ (µg·h/mL) Female	AUC ₀₋₂₄ (µg·h/mL) Female
10	Day 4	64.5	51.7	0.05
50	Day 4	165	164	0.18
250	Day 4	407	382	0.46
10	Day 12	69.1	69.8	0.06
50	Day 12	143	185	0.17
250	Day 12	294	375	0.4

Source: Applicant-generated table from Study Report T-09.617

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-09.617

Abbreviations: AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 hours; F0, Parental generation; F1, first generation of offspring or first filial generation; PPND, pre- and postnatal development

13.1.4. Other Toxicology/Specialized Studies

Phototoxicity: No phototoxicity studies was conducted with aprocitentan alone but an in vivo study conducted for macitentan (Study No: T-09.061) was referenced, which was deemed to be devoid of phototoxic potential, based on the lack of skin response. In this study administration of macitentan (0, 15 and 60 mg/kg, single, p.o.) in female hairless rats (Ico:OFA-hr/hr, 6/group) did not produce any erythema formation at an AUC_{0-24h} of 140 µg*hr/mL of aprocitentan at 60 mg/kg. This is approximately 4-fold the exposure at MRHD for aprocitentan.

13.1.5. Impurities/Degradants

(b) (4) and (b) (4) are degradation impurities present in both the aprocitentan drug substance and drug product. These impurities were reported to be formed by (b) (4). The Applicant proposed a specification limit of not more than (NMT) (b) (4) % and (b) (4) % for (b) (4) in drug substance and drug product, respectively, and

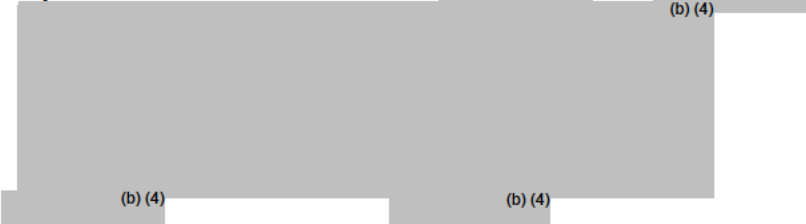
(b) (4) % for (b) (4) in drug substance, which exceeds the qualification thresholds per the International Council for Harmonisation (ICH) Q3A and ICH Q3B.

Mutagenic Potential Evaluation

(b) (4): The Applicant reported no structural alert for bacterial mutagenicity by conducted in silico analysis (Derek and Leadscope analysis) for (b) (4) and considered it as a Class 5 impurity as per ICH M7. To further support the lack of mutagenic potential for (b) (4) the Applicant conducted a bacterial mutagenicity assay (T-04.072) and it was submitted to NDA 204410. In this assay 5 bacterial strains (TA98, TA100, TA1535, TA1537 and TA102) were used and the (b) (4) was tested up to (b) (4) $\mu\text{g}/\text{plate}$ using the plate incorporation method (with or without metabolic activation). This assay was concluded to be negative for mutagenicity for (b) (4).

(b) (4): No mutagenicity data were provided for the (b) (4). However, this has a similar structure as (b) (4) (Fig 14).

Figure 15. Chemical Structures of (b) (4) and (b) (4)



Source: Applicant's submission—aprocitentan (ACT-132577) Drug Substance Impurities

CDER's Division of Applied Regulatory Science conducted (Q)SAR analysis to assess the potential mutagenicity of (b) (4). The internal (Q)SAR analysis predict no structural alerts for mutagenicity. Therefore, (b) (4) was considered to be nonmutagenic Class 5 impurity as per ICH M7. No additional genotoxicity evaluations were necessary.

General Toxicity

Drug substance impurities: To address the safety of (b) (4) and (b) (4), the Applicant provided a justification supporting reliance on the 39-week dog repeat dose toxicity study. In this study, (b) (4) and (b) (4) were reported to present at (b) (4) % and (b) (4) %, respectively, in the aprocitentan drug substance. According to the study report (Study # T-15.053) the levels reported were (b) (4) $\text{mg}/\text{kg}/\text{day}$ for (b) (4) and (b) (4) $\text{mg}/\text{kg}/\text{day}$ for (b) (4). The NOAEL (5 $\text{mg}/\text{kg}/\text{day}$) determined for aprocitentan in the 39-week repeat dose study in dogs yields (b) (4) $\text{mg}/\text{kg}/\text{day}$ (b) (4) and (b) (4) $\text{mg}/\text{kg}/\text{day}$ (b) (4). Human equivalent doses are thus (b) (4) mg/day (b) (4) and (b) (4) mg/day (b) (4), based on body surface area calculations assuming a 60 kg adult body weight. These doses are (b) (4) fold and (b) (4) fold (b) (4) the proposed drug substance specification limit of NMT (b) (4) % ((b) (4) mg) for (b) (4) and NMT (b) (4) % ((b) (4) mg) for (b) (4). Therefore, the proposed drug substance specifications are supported by the dog data and are considered acceptable.

Drug product impurities: To address the safety of drug product impurities, the Applicant provided a safety justification based on the 26-week rat repeat dose toxicity study. In this study,

(b) (4) was reported to at (b) (4) % in the aprocitentan. The NOAEL assigned for that study was 50 mg/kg/day, which yielding an (b) (4) dose of (b) (4) mg/kg/day. A human equivalent dose was calculated at (b) (4) mg/day, based on body surface area extrapolation for a 60 kg adult. This dose is ~ (b) (4)-fold (b) (4) the proposed drug substance specification limit of NMT at (b) (4) the proposed drug product specifications are supported by the rat data and are considered acceptable.

Table 71. Qualifications of Impurities in (b) (4) and (b) (4)

Impurity	Species/Study Duration	Levels in the Nonclinical Batch (%)	Amount (mg/kg/day) at the NOAEL	Human Equivalent Dose in mg/day (Based on BSA ³)	Proposed Limit mg/day (% for 25 mg)	Fold Difference/ Qualified?
(b) (4)	Dog/ 39 wk ¹	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) fold/yes
	Dog/ 39 wk ¹	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) fold/yes
	Rat/ 28 wk ²	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4) fold/yes

Source: Pharmacology/toxicology reviewer-generated table

¹ NOAEL is 5 mg/kg/day

² NOAEL is 50 mg/kg/day

³ BSA calculations are based on 60 kg adults.

Abbreviations: BSA, body surface area; NOAEL, no observed adverse effect level; wk, week

Overall, there are no nonclinical safety concerns with the levels of organic impurities at the MRHD.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

13.2.1. Embryo-Fetal Development

The initial NDA submission did not contain any EFD studies with aprocitentan alone. Instead, the Applicant relied upon macitentan [Opsumit NDA] EFD data in rats and rabbits, as agreed upon with the Agency. The macitentan EFD studies are discussed in Section 13.1.

During the review cycle, the Applicant submitted EFD studies conducted with aprocitentan alone to support their (b) (4) REMS proposal, which was submitted with the initial NDA package.

Rat Embryofetal Development Toxicity Study

Study Number/Title: T-22.030/ACT-132577E: ACT-132577E: An Embryo-Fetal Development Study by Oral (Gavage)

Key Study Findings

- Dose selection justification was insufficient (i.e., too low) to adequately characterize the potential developmental toxicity of aprocitentan.
- There were no treatment-related adverse effects at doses tested up to the highest dose of 10 mg/kg/day regarding maternal and developmental toxicity, which was associated with an AUC_{0-24 h} of 165000 ng*hr/mL for aprocitentan, approximately 5-fold the AUC at MRHD.
- While the minor observations in fetal visceral and skeletal examinations could not be attributed to aprocitentan treatment given similar observations reported in the control and historical control groups, fetal observations were similar to those reported in studies with the macitentan and other ERAs.

GLP Compliance: Yes

Table 72. Methods of Oral Embryo-Fetal Development Study in Rats

Parameter	Method Details
Dose and frequency of dosing	0, 1, 3, and 10 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% (w/v) methylcellulose (400 cP) and 0.5% (w/v/v) Tween 80 in ultrapure water
Species/strain	Time-mated Crl:WI(Han) Wistar Han female rats
Number/sex/group	22 females/group
Satellite groups	4 (control) to 12 (treatment) females/group for TK assessment
Study design	Female animals were dosed from Day 6 to Day 17 of gestation (inclusive). At last, females were euthanized on GD 21.
Deviation from study protocol affecting interpretation of results	The deviations listed may not affect the overall integrity of the study.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-22.030

Abbreviations: GD, gestational day; TK, toxicokinetics; w/v, weight by volume; w/v/v, weight by volume by volume

Table 73. Observations and Results of Embryo-Fetal Development Study in Rats

Parameters	Major Findings
Mortality	No mortality was observed
Clinical signs	No adverse clinical signs were observed
Body weights/ Food consumption	No effect on the body weight during the dosing interval GD 6 to 18 and at GD 21 was observed. Food consumption was reduced (12% at GD 6 to 9, 5% at GD 9 to 12 and 13% at GD 6 to 21).
Necropsy findings/ Cesarean section data	Macroscopic findings: No treatment-related adverse effects were observed. Ovarian and uterine examination and litter observations: The litter means for corpora lutea, implantations, percent pre-implantation loss, live and dead fetuses, early and late resorptions, percent postimplantation loss, fetal weight and the percentage of live male fetuses were not affected by the treatment. No abnormalities were noted in the placenta.

Parameters	Major Findings
Fetal evaluation	No treatment-related significant fetal external and visceral or skeletal malformations were observed at any dose levels compared to control or historical control data. Visceral examinations: Abnormal small testis was observed in fetus at 10 mg/kg/day, and it was not considered treatment-related because of the single observation; however, treatment effect cannot be ruled out completely. Skeletal examinations: One fetus in the control group was observed with multiple skeletal findings including one or more branched ribs and hemivertebra (arch and centrum) present at the 12th thoracic vertebra. One fetus in the 3 mg/kg/day group was observed with multiple skeletal findings including one or more small thoracic arches, fused thoracic centra, and one or more isolated ossification sites in the thoracic vertebrae. Other observations include skeletal ossification variations in the development of the ribs, skull bones, sternbrae, and vertebrae were considered not treatment-related due to the fact that similar observations were noticed in control animals. No dose relationship was established and/or the observations were within the historical control range.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-22.030
Abbreviations: ERAs, endothelin receptor antagonists; GD, gestational day

Justification for Dose Selection

A dose range-finding (DRF) study (Study No. T-22.029) was conducted for aprocitentan (0.3, 1, 3, 10 mg/kg/day) in rats. No mortality was observed in the DRF study. Reduction in food consumption (-21% between Day 6-18 and -15.7% between Day 6-21) was correlated with lower maternal body weight (4.3 to 9.2% at gestational day (GD) 6-9, 10 to 12.1% at GD 9-13, 6.8-9.7% on GD 7-17) at 10 mg/kg/day. Reduction in mean fetal body weights (7%, combined males and females) was observed at 10 mg/kg/day. Other observations including minor clinical signs (suspected dehydration, thin body appearance and hunched position) were not dose limiting. Except a slight reduction of mean fetal body weight (7%) at 10 mg/kg/day, no other treatment related effects were observed in ovarian and uterine examination and litter observations. No treatment related malformations or variations were observed. The Applicant selected 10 mg/kg/day as the highest dose based on a decrease in maternal body weight. Given the critical importance of identifying both a lowest-observed adverse effect level and a NOAEL for embryofetal toxicity with aprocitentan in the rat, doses selection was inadequate.

Rabbit Embryofetal Development Toxicity Study

Study Number/Title: T-22.028/ACT-132577E: An Embryo-Fetal Development Study by Oral (Stomach Tube) Administration in Rabbits

Key Study Findings

- No treatment-related adverse effect at doses tested up to 2.5 mg/kg/day for maternal toxicity and developmental toxicity, which was associated with a C_{max} of 51100 ng/mL and $AUC_{0-24 h}$ of 1000000 ng*hr/mL, approximately 29- fold the AUC at MRHD.

GLP Compliance: Yes

Table 74. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing	0, 0.25, 0.75 and 2.5 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% (w/v) methylcellulose (400 cP) and 0.5% (w/v/v) Tween 80 in ultrapure water
Species/strain	Rabbit/New Zealand white
Number/sex/group	20 per sex/group
Satellite groups	2 (control) to 8 (treatment) females/group TK
Study design	Dams treated once daily from GD 7-19. TK blood sampling was performed on gestation Days 7 and 19.
Deviation from study protocol affecting interpretation of results	The deviations listed may not affect the overall integrity of the study

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-22.028

Abbreviations: GD, gestational day; TK, toxicokinetics; w/v, weight by volume; w/v/v, weight by volume by volume

Table 75. Observations and Results of Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	Four animals were either dead or sacrificed early. One female was found dead (GD 22), and one female aborted (GD 27) its litter in the control group. Two females aborted (GD 22) their litter in the 0.75 mg/kg/day group. These findings were not considered treatment-related as they were only observed in control or low dose groups.
Clinical signs	No treatment-related significant adverse clinical signs were observed.
Body weights/Food consumption	No significant mean maternal body weight, mean maternal body weight gain, gravid uterine weights, or adjusted mean maternal body weights or mean maternal body weight gain were observed at any dose level. Food consumption was reduced 9% at GD10 to 13 in ≥ 2.5 mg/kg/day, between 13-23% at GD 13-16 in ≥ 0.25 mg/kg/day and 10-19% at GD 16 to 20 in ≥ 0.75 mg/kg/day groups.
Necropsy findings Cesarean section data	Macroscopic findings: No treatment related adverse findings were observed. Ovarian and uterine examination and litter observations: Mean fetal body weights were lower (8%) at 2.5 mg/kg/day compared to control. The litter means for corpora lutea, implantations, percent pre-implantation loss, live and dead fetuses, early and late resorptions, percent postimplantation loss, and fetal sex ratio were similar across the dose groups. No abnormalities were observed in the placenta.
Fetal evaluation	No treatment-related fetal external and visceral or skeletal malformations were observed at any dose levels. Minor observations were not considered treatment-related as they were either observed in the control group or with in the historical control data. Visceral examination: One fetus was observed with dilated aortic arch in control group. One fetus each in 0.75 and 2.5 mg/kg/day groups were observed with a persistent truncus arteriosus and a membranous ventricular septal heart defect. Skeletal examination: One fetus was observed with a hemivertebra with an arch, centrum and attached rib present at the tenth thoracic vertebra in the control group. Other observations include skeletal ossification variations in the development of the ribs, skull bones, sternbrae, and vertebrae were considered not treatment-related due to the similar observations in the control group or with in the historical control range.

Source: Pharmacology/toxicology reviewer-generated table based on Study Report T-22.028

Abbreviation: GD, gestational day

Justification for Dose Selection

A DRF study (Study # T-22.027) was conducted for aprocitentan (0.25, 0.75, 2.5 mg/kg/day) in rabbits. The Applicant referred to a nonpregnant rabbit study in which maximum tolerability of aprocitentan was tested. Based on the exposure ($AUC_{0-24\text{ h}}$ of 3740 $\mu\text{g}\cdot\text{hr}/\text{mL}$) observed at 10 mg/kg/day in this nonpregnant rabbit study, a dose of 2.5 mg/kg/day was selected as the highest dose for the DRF study with an aim to achieve one fourth of the exposure ($AUC_{0-24\text{ h}}$ of 935 $\mu\text{g}\cdot\text{hr}/\text{mL}$). In the DRF study, no mortality was observed. No treatment-related effects on body weight, food consumption, clinical signs, gravid uterine weights, maternal necropsy, ovarian and uterine parameters and litter parameters, fetal examination parameters were observed at doses tested, and an MTD could not be identified. The high dose tested achieved 29-fold the clinical exposure at the MRHD of 12.5 mg/day, which may be considered appropriate, though a lowest-observed adverse effect level for embryofetal toxicity could not be identified in the rabbit.

14. Clinical Pharmacology

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding

Study B-07.077

B-07.077 examined the plasma protein binding and plasma/red blood cell partitioning of aprocitentan in vitro using the ^{14}C -labelled derivative ACT-132577B in a concentration range from 0.1 to 300 $\mu\text{g}/\text{mL}$. The overall mean binding of ACT-132577B to plasma proteins over the whole concentration range in humans was 99%, with a mean free fraction of 1%. There was no obvious concentration-dependent effect in humans. Chromatogram radioactivity associated with ACT-132577B in the plasma and buffer compartments after radio-high pressure liquid chromatography showed that only about 90% of the plasma compartment radioactivity was associated with ACT-132577B, and in the buffer compartment, there were two main peaks that accounted for radioactivity. One peak corresponded to ACT-132577B and the other peak was an unknown chemical. This substance was on the radiochromatogram of ACT-132577 (in the starting material). The Applicant therefore believes that the compound in the dialysate is the result of a selective transfer during the equilibrium dialysis experiment and not a post-experimental degradation product. Therefore, the protein binding values were corrected based on the actual amount of ACT-132577. The corrected plasma protein binding was 99.5%, with a mean corrected free fraction of 0.5%. Plasma/red blood cell partitioning was determined at 500 ng/mL and 100 $\mu\text{g}/\text{mL}$. The mean association of radioactivity with red blood cells at both concentrations was 4.8%. The blood/plasma ratio was 0.54. This indicates that there was not a significant uptake of radioactivity into red blood cells.

14.1.2. Metabolism Studies

Study B-14.033

B-14.033 looked at the metabolic profile of aprocitentan in human liver preparations. Six metabolites were formed along two primary pathways involving hydrolysis to M1 and glucosidation to M3.

Incubation of radiolabeled aprocitentan, ACT-132577B, with human liver microsomes led to formation of M1 and M2 (4.3% and 2.1% of total chromatogram radioactivity, respectively). M1 was also observed in experiments without microsomes or a nicotinamide adenine dinucleotide phosphate (NADPH)-regenerating system and was present at 9.3% and 6.4% total chromatogram radioactivity, respectively, in comparable conditions.

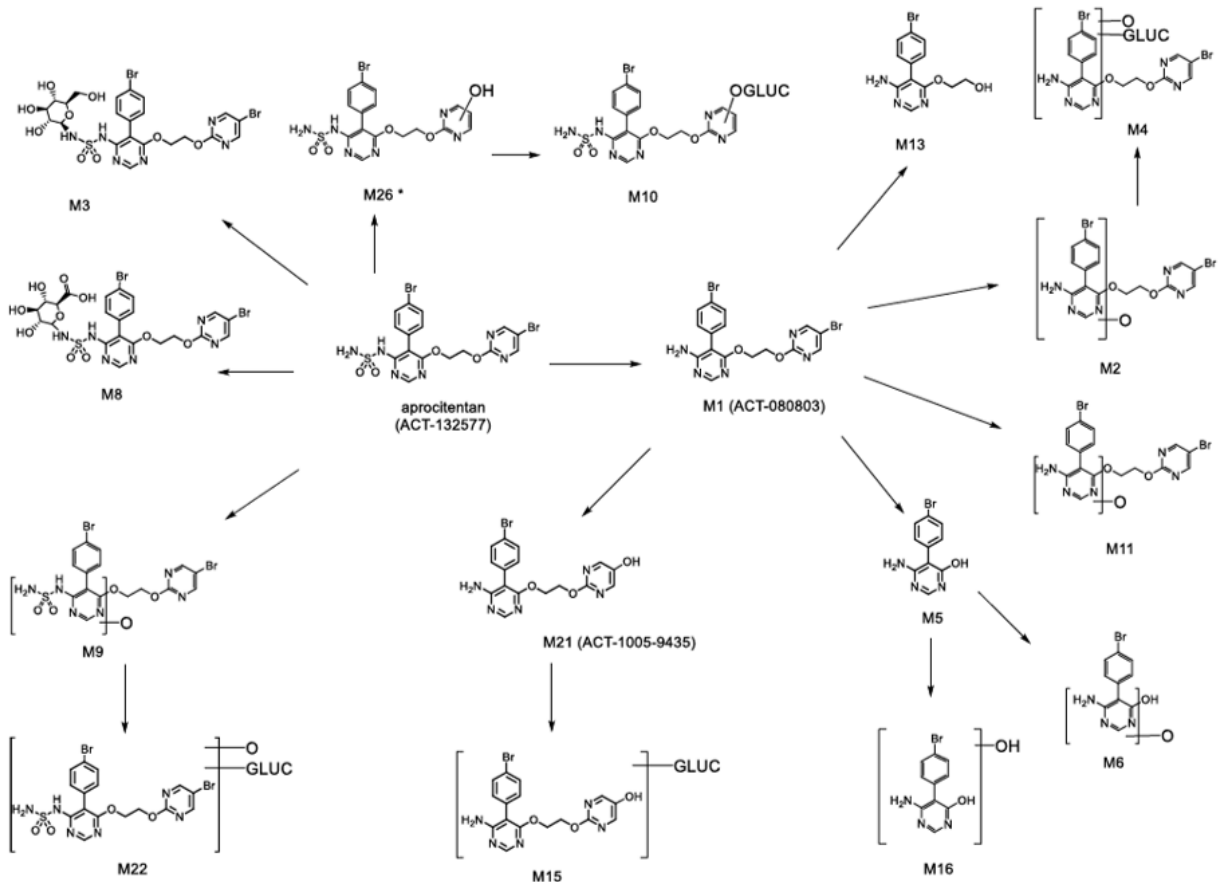
Incubation of ACT-132577B with hepatocytes generated metabolites M1-M6. No metabolite contributed to more than 5% total chromatogram radioactivity, and total turnover was 21%. Out of 3 batches, M1-M6 was seen in batch 1, and M1, M2, and M5 were seen in batches 2 or 3. M1 was seen in the control experiment without liver cells and accounted for 8.7% total chromatogram radioactivity after a 24-hour incubation.

Formation of M1 results from both chemical and enzymatic hydrolysis. M1 is then metabolized to secondary metabolites M2 and M5 through P450/FMO-dependent reactions. M2 undergoes further glucuronidation to M4, and M5 is oxidized to M6 in human hepatocytes.

Study B-14.050

This study determined the structure of aprocitentan metabolites with liquid chromatography combined with high resolution mass spectrometry. Specifically, structure determination of metabolites was performed from samples from the in vitro metabolite profiling study (B-14.033). Metabolites from rat hepatocytes were also characterized. The proposed metabolic pathways of aprocitentan are presented in [Figure 16](#). In total, it appears that aprocitentan is metabolized along 5 metabolic pathways – hydrolysis to M1, glucosidation to M3, glucuronidation to M8, oxidative debromination then glucuronidation to M10, and N-oxidation at the pyrimidine sulfamide moiety to M9. Metabolite M9 would then subsequently undergo glucuronidation to M22. M1 came from hydrolysis of the sulfamide moiety to an aminopyrimidine and has been shown to be a product of nonenzymatic hydrolysis and a true metabolite (See Study B-05.130 in Section [14.1.4](#)). Metabolites M9 and M26 undergo glucuronidation to metabolites M22 and M10, respectively. Additional downstream metabolites of M1 include M2, M11, M4, M21, M15, M5, M13, M6, and M16.

Figure 16. Proposed Metabolic Pathways of Aproцитентан



Source: Applicant-generated figure from Study B-14.050, Figure 3
Abbreviation: GLUC, glucuronic acid

Study B-18.023

B-18.023 was an in vitro study conducted to identify the human uridine diphosphate-glucuronosyltransferase (UGT) enzymes involved in the formation of the aproцитентан glucoside M3 metabolite. ¹⁴C-labelled aproцитентан was incubated with recombinant human UGT enzymes. UGT enzyme activity is listed in [Table 76](#). Aproцитентан was metabolized to M3 by UGT1A1 and UGT2B7. M3 formation was 1.1% for UGT1A1 and 1.4% for UGT2B7 after 60 mins, indicating turnover was low. Additionally, the chemical hydrolysis product M1 was the most prevalent entity observed in UGT experiments and control incubations without UDPG or UGT enzymes. M1 was similar in all samples ranging from 20 to 23% after 60 mins.

Table 76. Enzyme Activity of the Recombinant UGT Enzymes

UGT enzyme	batch no.	Marker reaction	UGT activity [pmol/(min·mg protein)]
UGT1A1	6320009	Estradiol 3-glucuronidation	770
UGT1A3	7065003	Estradiol 3-glucuronidation	150
UGT1A4	4310004	Trifluoperazine glucuronidation	1500
UGT1A6	5306001	7-OH-4-trifluoromethyl coumarin glucuronidation	10000
UGT1A9	6015001	7-OH-4-trifluoromethyl coumarin glucuronidation	4600
UGT2B4	7254003	7-OH-4-trifluoromethyl coumarin glucuronidation	360
UGT2B7	6209003	7-OH-4-trifluoromethyl coumarin glucuronidation	1300
UGT2B10	7157001	Amitriptyline glucuronidation	6.3
UGT2B15	5174006	7-OH-4-trifluoromethyl coumarin glucuronidation	2200

Source: Applicant generated table from Study B-18.023, Table 1
Abbreviations: no., number; UGT, uridine 5'-diphospho-glucuronosyltransferase

14.1.3. Transporter Characterization

Study B-17.068

B-17.068 is an in vitro drug transporter substrate and permeability study to determine if aproцитentan is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and to investigate the in vitro permeability of aproцитentan.

Efflux ratios of aproцитentan in MDCKII-MDR1 cells were 2.3 to 3.5 and decreased to 0.8-0.9 in the presence of zosuquidar, a selective P-gp inhibitor. In a few cases, the recoveries were below 70%, but the Applicant considers these samples valid since the Papp values were in agreement with the rest of the values. The data indicates that aproцитentan is a substrate of P-gp.

Efflux ratios of aproцитentan in MDCKII-BCRP cells were 7.3 to 23.2 and decreased to 0.8 to 1.3 in the presence of Ko143, a BCRP inhibitor. The data indicates that aproцитentan is a substrate of BCRP. In a few cases, the recoveries were below 70%, but the Applicant considers these samples valid since the Papp values were in agreement with the rest of the values. Overall, the data indicates that aproцитentan is a substrate of BCRP.

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The apparent absorptive permeability coefficients of aprocitentan in MDCKII cells were 13.6×10^{-6} cm/s, indicating moderate to high permeability.

Study B-10.642

Study B-10.642 evaluated if aprocitentan is a substrate of human hepatic organic anion transporting polypeptides (OATPs) OATP1B1, OATP1B3, and OATP2B1. Uptake of aprocitentan into wild-type and OATP-expressing CHO cells was high and rapid. There was no apparent difference in the uptake of aprocitentan between wild-type and OATP1B1 cells. The uptake of aprocitentan into OATP1B3 and OATP2B1 cells at concentrations less than $4\mu\text{M}$ was maximally 40% higher than into wild-type cells. No marked difference in the rate of uptake into wild-type and OATP1B1 cells was observed over 0.01 to $300\mu\text{M}$. The uptake ratios for OATP1B1, OATP1B3, and OATP2B1 were a maximum of 1.1, 1.3, and 1.4, respectively, with incubation times ranging from 0 to 60 seconds, and concentrations ranging from $1\mu\text{M}$ to $3\mu\text{M}$. The positive control of estrone-3-sulphate had an uptake ratio of 4.5, 5.6, and 11.6 for OATP1B1, OATP1B3, and OATP2B1, respectively, at 5 minutes at $5\mu\text{M}$. The data indicate that cellular uptake of aprocitentan does not depend on human OATP transporters but is driven by passive diffusion, though there may be some contribution from active uptake.

Additionally, aprocitentan inhibited OATP1B1-mediated uptake of atorvastatin and OATP1B3- and OATP2B1-mediated uptake of estrone-3-sulphate. The mean half maximal inhibitory concentration (IC_{50}) values for aprocitentan were 21, 56, and $15\mu\text{M}$ for OATP1B1, OATP1B3, and OATP2B1, respectively.

14.1.4. Drug-Drug Interactions

Study B-05.044

B-05.044 studied the effect of ACT-064992 (macitentan) and ACT-132577 (aprocitentan) on bile salt transport. Specifically, the potential to inhibit sodium-dependent taurocholate co-transporting polypeptide (NTCP) and human bile salt export pump (BSEP) was investigated. NTCP inhibition was tested in CHO F1p InTM cells over-expressing NTCP. BSEP inhibition was tested in Sf9 membrane vesicles over-expressing BSEP.

Aprocitentan inhibited NTCP- and BSEP-mediated uptake of taurocholic acid, with a mean IC_{50} value of $14\mu\text{M}$ and $50\mu\text{M}$, respectively.

Study B-05.130

B-05.130 studied a panel of cytochrome p450 (CYP) inhibition assays to assess the potential of drug-drug interactions with concomitantly administered CYP450 substrates. Specifically, the potential to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 was investigated. See [Table 77](#).

Table 77. In Vitro Inhibition Study Results

CYP Isoform	Medium	Marker	Reference	Results (μM)
1A2	Human liver microsomes	Phenacetin-o-de-ethylation	Furafulline	IC_{50} : >50
2A6		Coumarin 7-hydroxylation	8-Methoxy psoralen	IC_{50} : >100
2C9		Diclofenac 4'-hydroxylation	Sulfaphenazole	IC_{50} : 31 K_i : 11
2D6		Dextromethorphan-o-demethylation	Fluoxetine	IC_{50} : >100
2E1		Chlorzoxazone 6-hydroxylation	4-Methylpyrazole	IC_{50} : >100
3A4		Midazolam 1'-hydroxylation	Nicardipine	IC_{50} : 7.3
		Testosterone 6 β -hydroxylation	Nicardipine	IC_{50} : 11 K_i : 6.3
2B6	Recombinant enzyme expressed in baculovirus-transfected Sf9 cells	Substrate: ^{14}C -radiolabelled (S)-mephenytoin Marker: nirvanol (N-desmethylnmephenytoin)	Ticlopidine	IC_{50} : >100
2C19		Substrate: ^{14}C -radiolabelled (S)-mephenytoin Marker: 4-hydroxymephenytoin	Ticlopidine	IC_{50} : 15

Source: Reviewer-generated table

Abbreviations: ^{14}C , carbon 14 isotope; CYP, cytochrome p450; IC_{50} , half maximal inhibitory concentration; K_i , inhibitor constant

Study B-13.098

B-13.098 studied the inhibition potential of aprocitentan on P-gp activity in Caco-2 cells using digoxin as a prototypical substrate. Concentrations of aprocitentan ranged from 3 to 70 μM . Higher concentrations could not be studied due to limited solubility in the transport buffer. The absorptive permeability of digoxin increased in a concentration-dependent manner, as in the presence of 3 μM and 70 μM of aprocitentan, digoxin permeability increased by 1% and 35%, respectively.

Study B-20.030

B-20.030 assessed the inhibition potential of aprocitentan on the activity of OATP1B1 and OATP1B3 transporters in an assay with a pre-incubation period in CHO cells expressing each transporter. Aprocitentan inhibited OATP1B1 and OATP1B3 mediated uptake of atorvastatin acid with IC_{50} values of 19 and 27 μM , respectively. Cyclosporin A was used as a control inhibitor, and inhibited uptake of atorvastatin acid with IC_{50} values of 0.1 and 0.3 μM for OATP1B1 and OATP1B3, respectively. Nonspecific binding was assessed in CHO wild-type cells at concentrations of 19 and 27 μM , and the fraction recovered from incubation solutions was 45% and 83%.

Study B-17.069

B-17.069 assessed the potential of aprocitentan to alter the enzymatic activity of CYP2C8 and CYP2C9 due to time-dependent inhibition, as well as the inhibition potential of aprocitentan on the activity of UGT1A1 and UGT2B7. Experiments used human liver microsomes for CYP2C8, recombinant CYP2C9, and recombinant UGT enzymes for UGT1A1 and UGT2B7. The marker reactions for UGT1A1 and UGT2B7 were estradiol 3- β -glucuronidation and 3'-azido-3'-

deoxythymidine 5- β -glucuronidation, respectively. Paclitaxel 6 α -hydroxylation was used as a marker reaction for CYP2C8, and formation of 4-hydroxymephenytoin was monitored as a marker for CYP2C19 activity. Gemfibrozil 1-O- β glucuronide and ticlopidine were reference inhibitors of CYP2C8 and CYP2C19, respectively. IC₅₀ shift was determined as the ratio of the IC₅₀ values without and with NADPH and indicates the change in enzyme activity during the pre-incubation period. The IC₅₀ shift for aprocitentan in CYP2C8 was 1.0 and was not determined in CYP2C19 because the IC₅₀ with pre-incubation with and without NADPH were both >100 μ M, whereas the IC₅₀ shift for gemfibrozil 1-O- β -glucuronide and ticlopidine for CYP2C8 and CYP2C19 was 24 and 7.8, respectively. This indicates that aprocitentan is not a time-dependent inhibitor of CYP2C8 and CYP2C19. Aprocitentan was a weak inhibitor of UGT1A1 and UGT2B7, with IC₅₀ values of 23 and 43 μ M, respectively. Nonspecific binding of aprocitentan in the UGT inhibition assays was 3.9% and 3.8% for UGT1A1 and UGT2B7, respectively.

Study B-21.017

B-21.017 assessed the time-dependent inhibition of CYP1A1 and CYP2B6 by aprocitentan in human liver microsomes. Marker reactions for CYP1A2 and CYP2B6 were phenacetin-O-deethylation and bupropion hydroxylation, respectively. Furaflavone and ticlopidine were run in parallel as positive controls for CYP1A2 and CYP2B6, respectively. IC₅₀ shift was determined as the ratio of the IC₅₀ values without and with NADPH and indicate the change in enzyme activity during the pre-incubation period. The IC₅₀ shift for aprocitentan in CYP1A2 and CYP2B6 was not determined, as values with and without NADPH were >100 μ M, whereas the IC₅₀ shift for furaflavone and ticlopidine for CYP1A2 and CYP2B6 was 94 and 131, respectively. This indicates that aprocitentan is not a time-dependent inhibitor of CYP1A2 and CYP2B6.

Study B-05.107

B-05.107 assessed the potential of aprocitentan to induce human CYP3A4, CYP2C9, and CYP1A2. Activation of the human pregnane X receptor (PXR) by aprocitentan was tested in a reporter gene assay, and induction of CYP3A4, CYP2C9, and CYP1A2 was tested in three batches of primary human hepatocytes on an mRNA and/or enzyme activity level. Nifedipine, diclofenac, and phenacetin were used as marker substrates for CYP3A4, CYP2C9, and CYP1A2 activity, respectively. Rifampicin was a positive control in the PXR activation assay. Aprocitentan was tested for induction at concentration up to 10 μ M. The positive control for the CYP3A4 and CYP2C9 regulation assays was rifampicin, and the positive control for the CYP1A2 regulation assay was omeprazole.

Aprocitentan activated PXR with a half maximal effective concentration (EC₅₀) of 7.2 to 8.7 μ M, which is less potent than the positive control rifampicin (EC₅₀ 0.5 to 0.6 μ M). Aprocitentan demonstrated generally concentration-dependent increases in CYP3A4 mRNA and enzyme activity. In the first batch of hepatocytes, the fold activity was 1.36, 1.57, 2.90, and 3.87 at 0.1, 1, 3, and 10 μ M, respectively. In the second batch of hepatocytes, the fold activity was 0.99, 1.13, 1.42, and 1.36 at 0.1, 1, 3, and 10 μ M, respectively. In the third batch of hepatocytes, the fold activity was 1.35, 1.47, 1.51, and 1.28 at 0.1, 1, 3, and 10 μ M, respectively. CYP3A4 mRNA levels also increased dose dependently, with 10 μ M producing a 6.72-, 2.77-, and 2.84-fold induction in each hepatocyte batch compared to a 9.59-, 5.30-, and 4.89-fold induction in each

hepatocyte batch for 10 μ M rifampicin. There were no dose-dependent increases in CYP2C9 activity; however, it does appear that there was a small dose-dependent increase in CYP2C9 mRNA levels. The 10 μ M dose produced a 1.59-, 1.25-, and 1.29-fold induction in each hepatocyte batch compared to a 2.42-, 2.04-, and 2.90-fold induction at 10 μ M rifampicin. There were dose-dependent increases in CYP1A2 activity with increasing aprocitentan dose. The 10 μ M dose produced a 3.05-, 2.28- and 2.71-fold increase in activity, compared to a 19.73-, 14.23-, and 10.83-fold increase in activity with omeprazole.

Study B-12.103

B-12.103 assessed the potential for aprocitentan to competitively inhibit CYP2C8 and time-dependent inhibition of CYP2D6 and CYP3A4 in vitro using human liver microsomes and cytochrome P450 isoform-specific marker transformations. The reactions used paclitaxel 6 α -hydroxylation, diclofenac 4'-hydroxylation, dextromethorphan-O-demethylation, and testosterone 6 β -hydroxylation as marker reactions for CYP2C8, CYP2C9, CYP2D6, and CYP3A4, respectively. Reference inhibitors included quercetin, tienilic acid, paroxetine, and mibefradil for CYP2C8, CYP2C9, CYP2D6, and CYP3A4 respectively.

Aprocitentan was an inhibitor of CYP2C8 activity (IC_{50} =23 μ M). Aprocitentan had no time-dependent inhibition of CYP2C9, CYP2D6, or CYP3A4 activities, as the shift values were 1.2, 0.9, and not calculable due to absence of inhibition, respectively, compared to reference shift values of 190, 64, and 29, respectively.

Study B-13.097

Study B-13.097 assessed the inhibition potential of aprocitentan on the activity of efflux and uptake organic anion transporters (OATs) OAT1 and OAT3, organic cation transporters (OCTs) OCT1 and OCT2, multidrug and toxin extrusion transporters (MATE)-1 and MATE2K, and BCRP. Probe substrates (μ M) were MPP⁺ (5), pulmonary arterial hypertension (10), furosemide (5), MPP⁺ (5), metformin (50), and 4-(4-dimethylaminostyryl)-N-methylpyridinium (1), and positive control inhibitors (μ M) were repaglinide (600), probenecid (100), probenecid (100), imipramine (300), cimetidine (100), and ondansetron (100) for OCT-1, OAT1, OAT3, OCT2, MATE1, and MATE2K, respectively. For BCRP assessment in BCRP-MDCK cells, cladribine was used as a probe substrate, and Ko143 was used as a positive control inhibitor.

Aprocitentan showed inhibitory potential for OAT1 (IC_{50} =4.7 μ M). Aprocitentan also showed inhibitory potential of BCRP (IC_{50} =5.7 μ M). Aprocitentan had some inhibition in a concentration-dependent manner for OAT3 (IC_{50} =1.5 μ M). There was no effect observed on OCT1, OCT2, or MATE2K or MATE1 at the concentrations tested (up to 100 μ M).

14.1.5. In Vitro Summary

Plasma protein binding of aprocitentan in humans was 99.5%, and the mean blood/plasma ratio was 0.54, indicating limited binding to red blood cells. Aprocitentan was highly permeable across cell membranes. When studies were conducted to determine if aprocitentan is dependent on hepatic uptake transporters OATP1B1 and OATP1B3, the uptake of aprocitentan in wild-type and OATP-expressing cells was high and rapid without much difference between the two cell

line types, indicating that hepatic uptake of aprocitentan is mostly due to passive diffusion. Aprocitentan is a substrate of P-gp and BCRP; however, aprocitentan has high permeability across cell membranes, and PK was dose-proportional up to 100 mg, indicating a limited role for efflux transporters in oral absorption. Further, aprocitentan was mostly metabolized prior to excretion. Therefore, impact on aprocitentan exposure due to P-gp or BCRP inhibitors affecting absorption or excretion is not expected. Only 0.2% of the administered dose was excreted unchanged in the urine, so change in uptake and efflux by renal transporter inhibitors or inducers would not likely have clinical relevance.

Aprocitentan inhibited uptake of several model substrates for several drug transport proteins, with the strongest inhibition seen on OAT1/3 and BCRP (IC_{50} values ranging from 1.5 to 5.7 μ M). Inhibition of OATP, NTCP, and bile salt export pump was also observed, but to a lesser extent (IC_{50} values ranging from 14 to 50 μ M). IC_{50} values for P-gp, OCT_{1/2}, or MATE1/2K were around or above the highest tested concentration. It was determined in vitro that aprocitentan does not inhibit P-gp because the intestinal luminal concentration of the interacting drug/ IC_{50} is 1.83 for a 25 mg dose of aprocitentan, which is less than the threshold of 10. BCRP showed potential to inhibit BCRP in vitro because the intestinal luminal concentration of the interacting drug/ IC_{50} value was 32 for a 25 mg dose of aprocitentan, which is greater than the threshold of 10. A clinical drug-drug interaction study for BCRP was conducted (see Section 14.2). R values for OATP1B1 and OATP1B3 were 1.007 and 1.003, respectively, which is below the cutoff of 1.1, indicating that aprocitentan does not have the potential to inhibit OATP1B1 and OATP1B3. OAT1 and OAT3 $I_{max,u}/IC_{50}$ values were 0.026 and 0.083, respectively. As these values are lower than the cutoff of 0.1, aprocitentan does not inhibit OAT. As the IC_{50} for OCT and MATE were >100 μ M, aprocitentan does not inhibit these transporters.

Metabolite M1 is formed by hydrolysis and was formed with and without the presence of enzymes. In human hepatocytes, 6 metabolites were found across all batches (M1-M6). M1 was present in the highest concentrations, followed by secondary and tertiary metabolites M2, M5, M4, and M6. The M3 glucoside metabolite was seen in a single hepatocyte batch at lower levels than the other observed metabolites. UGT1A1 and UGT2B7 were shown to catalyze the formation of M3.

Aprocitentan had no or minimal inhibition on most human CYP enzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP2E1. All members of the CYP2C family were inhibited, with IC_{50} values ranging from 15 to 31 μ M. A K_i value of 11 μ M was determined on CYP2C9. Aprocitentan also inhibited CYP3A4 in vitro for both the midazolam and testosterone markers, with IC_{50} values of 7.3 μ M and 11 μ M, respectively. Aprocitentan did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in a time-dependent manner. Aprocitentan inhibited UGT1A1 and UGT2B7 (IC_{50} values of 23 μ M and 43 μ M, respectively). For CYP3A4, assuming a conservative unbound fraction in plasma of 1% and a correction of K_i for the fraction of unbound drug in the test system by 0.8 (in vitro tests indicated values between 0.8 and 1.0), the R_1 and $R_{1,gut}$ values for CYP3A4 were 1.01 and 37, respectively. The R_1 value was below the recommended threshold of 1.02, but the $R_{1,gut}$ value was above the threshold of 11. A clinical drug-drug interaction study for CYP3A4 was conducted (Section 14.2).

Aprocitentan activated human PXR with an EC_{50} of 7.2 to 8.7 μ M. Concentration-dependent increases in CYP3A4 mRNA and enzyme activity were observed. CYP3A4 activity was

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increased by up to 3.9-fold, and CYP3A4 mRNA was increased by up to 6.7-fold at the highest aprocitentan concentration (10 μ M), though no relevant changes in CYP1A2 and CYP2C9 activity were observed. Of note, the expected aprocitentan $C_{\max,u}$ at steady state is about 0.07 μ M.

14.2. In Vivo Studies

Study AC-080-101: Single-Center, Three-Part Phase 1 Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ACT-132577 in Healthy Male and Female Subjects

Study Design

This three-part Phase 1 study was composed of Part A, an open-label, single-dose, Phase 1 pilot study; Part B, a double-blind, randomized, placebo-controlled parallel-group, single ascending dose Phase 1 study (including food effect); and Part C, a double-blind, randomized, placebo-controlled, parallel-group, multiple ascending dose Phase 1 study (including healthy elderly subjects). This study used aprocitentan in capsules.

In Part A, PK, safety, and tolerability was assessed for a single 5 mg dose. In Part B, PK was assessed for single doses of 25, 100, 300, or 600 mg. Food effect was also assessed. In Part C, multiple doses of aprocitentan in healthy male and female subjects were assessed. Doses studied included 5, 25, or 100 mg administered for 10 days. PK in elderly subjects were also assessed.

Results

After a single dose, aprocitentan was more rapidly absorbed at lower doses than higher doses, with a median $T_{\max}$ of 3 hours after a single 5 mg dose compared to 9 hours after a single 600 mg dose ([Table 78](#)). After a single dose, $C_{\max}$ and $AUC_{0-\infty}$ were less than dose proportional ([Table 78](#)).

Table 78. Summary of PK Parameters of Aprocitentan by Treatment

Parameter [unit]	Statistics	Part A	Part B	Part B	Part B	Part B	Part B
		ACT-132577 5 mg (N = 6)	ACT-132577 25 mg (N = 6)	ACT-132577 100 mg (N = 6)	ACT-132577 100 mg fed (N = 5)	ACT-132577 300 mg (N = 6)	ACT-132577 600 mg (N = 6)
t_{max} [h]	N/missing	6/0	6/0	6/0	5/0	6/0	6/0
	Median	3.00	4.00	9.00	5.00	8.50	9.00
	Min,Max	3.0, 5.0	4.0, 4.0	4.0, 10.0	5.0, 12.0	4.0, 24.1	4.0, 36.0
C_{max} [$\mu\text{g}/\text{mL}$]	N/missing	6/0	6/0	6/0	5/0	6/0	6/0
	Geometric mean	0.35	1.58	3.76	5.98	10.82	14.09
	95% CI of geometric mean	0.25, 0.49	1.28, 1.95	2.96, 4.77	5.10, 7.01	7.08, 16.54	10.79, 18.40
AUC_{0-t} [$\mu\text{g}^*\text{h}/\text{mL}$]	N/missing	6/0	6/0	6/0	5/0	6/0	6/0
	Geometric mean	17.74	78.09	244.14	292.63	776.14	1273.57
	95% CI of geometric mean	13.60, 23.13	61.62, 98.97	191.04, 312.00	195.99, 436.92	504.99, 1192.87	853.61, 1900.14
$AUC_{0-\infty}$ [$\mu\text{g}^*\text{h}/\text{mL}$]	N/missing	6/0	6/0	6/0	5/0	6/0	6/0
	Geometric mean	18.32	80.73	254.26	304.10	800.72	1339.46
	95% CI of geometric mean	14.13, 23.75	62.86, 103.66	198.20, 326.18	206.83, 447.14	516.97, 1240.20	887.25, 2022.14
$t_{1/2}$ [h]	N/missing	6/0	6/0	6/0	5/0	6/0	6/0
	Geometric mean	41.32	44.95	46.84	50.50	42.92	44.26
	95% CI of geometric mean	36.88, 46.29	37.42, 54.00	40.16, 54.63	39.02, 65.36	39.21, 46.99	40.89, 47.92

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-1
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t; CI, confidence interval; C_{max} , maximum concentration; max, maximum; min, minimum; N, overall number of subjects; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration

Generally, females had higher plasma concentrations, with C_{max} and $AUC_{0-\infty}$ values that were about 1.3-fold higher than males (Table 79).

Table 79. Effects of Sex on Plasma PK Variables After a Single Dose of Aprocitentan

Parameter [unit]	Statistics	
C_{max} [$\mu\text{g}/\text{ml}$]	N/missing	30/0
	Ratio of geometric means (females/males)	1.25
	90% CI of the ratio	1.04, 1.49
$AUC_{(0-\infty)}$ [$\mu\text{g}^*\text{h}/\text{mL}$]	N/missing	30/0
	Ratio of geometric means (females/males)	1.27
	90% CI of the ratio	1.07, 1.52

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-6
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max} , maximum concentration; N, overall number of subjects; PK, pharmacokinetics

After multiple-dose administration, steady-state conditions were reached by Day 8. Accumulation was about 3-fold, and C_{max} and AUC_{τ} were dose-proportional (Table 80).

Table 80. Dose Proportionality After Multiple Doses

Parameter [unit]	Statistics	Slope of predicted dose proportionality	Critical interval for slope
$C_{\max(\text{LDI})}$ [ng/ml]	N/missing	17/0	
	Slope estimate	0.93	
	90% CI of estimate	0.85462, 1.00000	0.77, 1.23
	p-value	<.0001	
$AUC_{\tau(\text{LDI})}$ [ng*h/mL]	N/missing	17/0	
	Slope estimate	0.94	
	90% CI of estimate	0.87163, 1.01568	0.77, 1.23
	p-value	<.0001	

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-9
Dose proportionality would be declared when the 90% CI for slope lies completely within the critical interval $(1+\log_e(0.5))\log_e(r)$, $1+\log_e(2)/\log_e(r)$, where r = highest dose/lowest dose ($r=100/5=20$)
Abbreviations: AUC_{τ} , area under the concentration-time curve over a dosing interval; CI, confidence interval; $C_{\max}$, maximum concentration; N, overall number of subjects; LDI, last dosing interval

$C_{\max}$ and AUC_{τ} were higher in females compared to males, with values approximately 1.3- to 1.4-fold of those seen in males (Table 81).

Table 81. Effects of Sex on Plasma PK Variables After Multiple Doses of Aprocitentan in Healthy Adult and Elderly Subjects

Parameter [unit]	Statistics
$C_{\max(\text{FDI})}$ [$\mu\text{g}/\text{mL}$]	N/missing 23/0
	Ratio of geometric means (females/males) 1.29
	90% CI of the ratio 1.09, 1.53
$C_{\max(\text{LDI})}$ [$\mu\text{g}/\text{mL}$]	N/missing 23/0
	Ratio of geometric means (females/males) 1.38
	90% CI of the ratio 1.18, 1.60
$AUC_{\tau(\text{FDI})}$ [$\mu\text{g}\cdot\text{h}/\text{mL}$]	N/missing 23/0
	Ratio of geometric means (females/males) 1.32
	90% CI of the ratio 1.14, 1.52
$AUC_{\tau(\text{LDI})}$ [$\mu\text{g}\cdot\text{h}/\text{mL}$]	N/missing 23/0
	Ratio of geometric means (females/males) 1.37
	90% CI of the ratio 1.21, 1.56

Source: Applicant-generated table from AC-08-101 Study Report, Doc No D-15.519, Table 11-13
Abbreviations: AUC_{τ} , area under the concentration-time curve over a dosing interval; CI, confidence interval; $C_{\max}$, maximum concentration; FDI, first dosing interval; N, overall number of subjects; LDI, last dosing interval; PK, pharmacokinetic

Elderly subjects (inclusion criteria: 65-80 years, inclusive) had a higher $C_{\max}$ and AUC_{τ} compared to nonelderly subjects (inclusion criteria: 18-45 years, inclusive), with values 1.3- and 1.2-fold higher after the last dosing interval, respectively (Table 82). In healthy elderly females, $C_{\max}$ and AUC_{τ} were approximately 1.6-fold higher than those of healthy elderly males.

Table 82. Multiple Dosing Age Effect

Parameter [unit]	Statistics	
$t_{\max(\text{FDI})}$ [h]	N/missing	11/0
	Median of difference (elderly-non-elderly)	-0.50
	90% CI of the median	-3.00, 2.00
$t_{\max(\text{LDI})}$ [h]	N/missing	11/0
	Median of difference (elderly-non-elderly)	-1.50
	90% CI of the median	-4.00, 2.00
$C_{\max(\text{FDI})}$ [ng/ml]	N/missing	11/0
	Ratio of geometric means (elderly/non-elderly)	1.21
	90% CI of the ratio	0.85, 1.73
$C_{\max(\text{LDI})}$ [ng/ml]	N/missing	11/0
	Ratio of geometric means (elderly/non-elderly)	1.31
	90% CI of the ratio	0.97, 1.78
$AUC_{\tau(\text{FDI})}$ [ng*h/mL]	N/missing	11/0
	Ratio of geometric means (elderly/non-elderly)	1.20
	90% CI of the ratio	0.87, 1.66
$AUC_{\tau(\text{LDI})}$ [ng*h/mL]	N/missing	11/0
	Ratio of geometric means (elderly/non-elderly)	1.21
	90% CI of the ratio	0.92, 1.58
$t_{1/2}$ [h]	N/missing	11/0
	Ratio of geometric means (elderly/non-elderly)	1.07
	90% CI of the ratio	1.00, 1.16

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-10
Abbreviations: AUC_{τ} , area under the concentration-time curve over a dosing interval; CI, confidence interval; $C_{\max}$, maximum concentration; FDI, first dosing interval; N, overall number of subjects; LDI, last dosing interval; $t_{1/2}$, terminal half-life; $t_{\max}$, time to reach maximum concentration

ET-1 levels increased with doses of 25 mg aprocitentan and above ([Table 83](#)). ET-1 values were similar between males and females ([Table 84](#)).

Table 83. Summary of ET-1 Values by Treatment

Parameter [unit]	Statistics	ACT-132577	ACT-132577	ACT-132577	Placebo
		5 mg	25 mg	100 mg	
		(N = 6)	(N = 6)	(N = 5)	(N = 5)
AUC _{τ(FDI)} [pg*h/mL]	N/missing	6/0	6/0	5/0	5/0
	Geometric mean	27.91	36.98	44.34	30.34
	95% CI of geometric mean	20.77, 37.49	32.31, 42.34	38.19, 51.48	26.02, 35.39
AUC _{τ(LDI)} [pg*h/mL]	N/missing	6/0	6/0	5/0	5/0
	Geometric mean	33.19	53.14	81.09	31.02
	95% CI of geometric mean	23.40, 47.06	42.95, 65.73	66.21, 99.32	26.46, 36.36

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-14
Abbreviations: AUC_τ, area under the concentration-time curve over a dosing interval; CI, confidence interval; ET, endothelin; FDI, first dosing interval; N, overall number of subjects; LDI, last dosing interval

Table 84. Comparison of Sex Effect on ET-1

Parameter [unit]	Statistics
AUC _{τ(FDI)} [pg*h/mL]	N/missing
	Ratio of geometric means (females/males)
	90% CI of the ratio
AUC _{τ(LDI)} [pg*h/mL]	N/missing
	Ratio of geometric means (females/males)
	90% CI of the ratio

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-15
Abbreviations: AUC_τ, area under the concentration-time curve over a dosing interval; CI, confidence interval; ET, endothelin; FDI, first dosing interval; N, overall number of subjects; LDI, last dosing interval

Exposure increased with food, with geometric mean ratios (fed/fasted) of 1.73 and 1.23 for C_{max} and AUC_{τ-∞} (Table 85).

Table 85. Effects of Food on Plasma PK Variables After a Single 100 mg Dose of Aprocitentan

Parameter [unit]	Statistics	
t_{max} [h]	N/missing	5/0
	Median of difference (fed/fasted)	-1.00
	90% CI of the median	-4.00, 1.50
C_{max} [ng/ml]	N/missing	5/0
	Ratio of geometric means (fed/fasted)	1.73
	90% CI of the ratio	1.51, 1.98
$AUC_{(0-t)}$ [ng*h/mL]	N/missing	5/0
	Ratio of geometric means (fed/fasted)	1.24
	90% CI of the ratio	1.07, 1.43
$AUC_{(0-\infty)}$ [ng*h/mL]	N/missing	5/0
	Ratio of geometric means (fed/fasted)	1.23
	90% CI of the ratio	1.07, 1.41
$t_{1/2}$ [h]	N/missing	5/0
	Ratio of geometric means (fed/fasted)	1.05
	90% CI of the ratio	0.96, 1.15

Source: Applicant-generated table from AC-080-101 Study Report, Doc No D-15.519, Table 11-2
 Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t; CI, confidence interval; C_{max} , maximum concentration; N, overall number of subjects; PK, pharmacokinetics, $t_{1/2}$, time to reach maximum concentration, t_{max} , time to reach maximum concentration

After multiple-dose administration, mean increases from baseline in body weight were observed in aprocitentan groups, especially in the 100 mg dose group and the elderly group, where the mean change in body weight ranged from -0.5 to +2.5 kg during the study. The placebo group mean change from baseline ranged from -1.1 to +0.9 kg. Following multiple doses of 5, 25, or 100 mg aprocitentan, there was a mean decrease in hemoglobin from baseline of 0.53 to 1.54 g/dL. Mean decreases from baseline in those receiving placebo ranged from 0.22 to 1.22 g/dL. The decrease appears to be dose-related, with median decreases from baseline of 1, 1.3, and 1.6 g/dL for 5, 25, and 100 mg doses, respectively. The median decrease in hemoglobin for those on placebo was 1.1. There were also decreases in hematocrit and red blood cells.

Agency Assessment

Aprocitentan exposure increased with food and was higher in females and the elderly. Aprocitentan is intended for chronic use and these differences in AUC are relatively minor; therefore, no dosage adjustments are warranted for food, sex, or age. At steady state, there were treatment- and dose-related decreases in hemoglobin and hematocrit, and after multiple doses of 100 mg aprocitentan, body weight increased more compared to subjects receiving placebo.

Study AC-080-104: Single-Center, Open-Label Study With ¹⁴C-Radiolabeled ACT-132577 to Investigate the Mass Balance, Pharmacokinetics, and Metabolism Following Single Oral Administration to Healthy Male Subjects

Study Design

This study was a single-center, open-label mass balance study with ¹⁴C-radiolabeled aprocitentan. A single oral dose of aprocitentan was administered in a capsule, followed by an observation period of 14 days where blood, urine, and feces samples were collected.

Results

The mean age of the 6 enrolled subjects was 63.0 years (range 61-64 years) with a mean body mass index of 25.23 kg/m² (range 22.2-27.2 kg/m²). After administration, 52.12% of the administered dose was recovered in the urine, and 24.79% of the administered dose was recovered in the feces. Total cumulative recovery ranged from 65.8% to 82.9%, with 5 out of 6 subjects having a total cumulative recovery of $\geq 75\%$.

Exposure to ¹⁴C-radioactivity was lower in whole blood compared to plasma, and the estimated blood/plasma ratio based on C_{max} and AUC_{0-∞} was 0.59 and 0.63, respectively. The mean C_{max} (966 ng/mL) and median T_{max} (5.0 h) of aprocitentan in plasma were comparable to that of ¹⁴C-radioactivity (mean C_{max} 1060 ng eq/mL; median T_{max} 4.0 h) ([Table 86](#) and [Table 87](#)).

Table 86. Summary of PK Parameters of Total ¹⁴C-Radioactivity in Whole Blood and Plasma

Parameter [unit]	Statistics	Total ¹⁴ C radioactivity (whole blood)	Total ¹⁴ C radioactivity (plasma)
		(N = 6)	(N = 6)
C _{max} [ng-eq/mL]	N/miss	6/0	6/0
	Geom. mean	624	1060
	95% CI of geom. mean	566, 688	929, 1210
t _{max} [h]	N/miss	6/0	6/0
	Median	6.00	4.00
	Min, Max	3.0, 12.0	3.0, 8.0
AUC _{0-t} [ng-eq*h/mL]	N/miss	6/0	6/0
	Geom. mean	49183	80767
	95% CI of geom. mean	43907, 55093	71777, 90884
AUC _{0-∞} [ng-eq*h/mL]	N/miss	6/0	6/0
	Geom. mean	54027	84822
	95% CI of geom. mean	47652, 61254	75778, 94945
t _{1/2} [h]	N/miss	6/0	6/0
	Geom. mean	150.5	110.6
	95% CI of geom. mean	112.4, 201.5	90.6, 135.0

Source: Applicant-generated table from AC-080-104 Study Report, Doc No D-18.105, Table 11-2
Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t; CI, confidence interval; C_{max}, maximum concentration; ¹⁴C, carbon 14 isotope; geom., geometric; miss, missing; N, overall number of subjects; PK, pharmacokinetics, t_{1/2}, time to reach maximum concentration, t_{max}, time to reach maximum concentration

Table 87. Summary of PK Parameters of Aprocitentan in Plasma

Parameter [unit]	Statistics	ACT-132577 (plasma)
		(N = 6)
C_{max} [ng/mL]	N/miss	6/0
	Geom. mean	966
	95% CI of geom. mean	887, 1053
t_{max} [h]	N/miss	6/0
	Median	5.00
	Min, Max	4.0, 12.0
AUC_{0-t} [ng*h/mL]	N/miss	6/0
	Geom. mean	61692
	95% CI of geom. mean	55793, 68215
$AUC_{0-\infty}$ [ng*h/mL]	N/miss	6/0
	Geom. mean	62192
	95% CI of geom. mean	56215, 68805
$t_{1/2}$ [h]	N/miss	6/0
	Geom. mean	48.1
	95% CI of geom. mean	44.3, 52.3

Source: Applicant-generated table from AC-080-104 Study Report, Doc No D-18.105, Table 11-3
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t; CI, confidence interval; C_{max} , maximum concentration; geom., geometric; miss, missing; N, overall number of subjects; PK, pharmacokinetics, $t_{1/2}$, time to reach maximum concentration, t_{max} , time to reach maximum concentration

In plasma, aprocitentan was mostly detected unchanged (94.3% of the total radioactivity of the sample). The only detected metabolite with a relative abundance of more than 1% of the total radioactivity was metabolite M29 (4.5% of the total radioactivity of the sample).

In urine, the main products were M3 (46.4% total radioactivity), M6 (8.5% total radioactivity), M16 (8.2% total radioactivity), and A1 (9.7% total radioactivity). In feces, the main products were M1 (41.5% total radioactivity), and unchanged aprocitentan (27.4% total radioactivity) ([Table 88](#)).

There were two metabolic pathways that contributed to 25% or more of the ^{14}C -radioactive elimination: glucosidation to M3 accounting for 25.2% of the administered dose (24.3% urine, 0.8% feces), and hydrolysis of the sulfamide moiety to the corresponding aminopyrimidine of aprocitentan to M1 (10.3% feces, 1.7% urine). After formation of M1, several reactions occur, such as cleavage to M13 (0.8% urine) with further oxidation to A1 (5.1% urine, 1.3% feces), cleavage to M5 (0.7% urine) followed by oxidation of M6 (4.5% urine) and M16 (4.3% urine, 0.4% feces). Other metabolites formed from M1 include A4 (0.2% feces), A5 (0.8% feces), M4

(0.9% urine), and M11 (0.4% feces). Overall, elimination through M1 and its metabolites accounted for 31.5% of the administered dose.

Table 88. Excretion of Unchanged Aprocitentan and its Metabolites in Urine and Feces

Compound	Percent of radioactivity				
	Urine		Feces		Urine + feces
	in the sample (%)	of the administered dose (%)	in the sample (%)	of the administered dose (%)	
Total ¹		52.4		24.9	
ACT-132577	0.3	0.2	27.4	6.8	7.0
M1	3.3	1.7	41.5	10.3	12.1
M3	46.4	24.3	3.4	0.8	25.2
M4	1.8	0.9			0.9
M5	1.3	0.7	--	--	0.7
M6	8.5	4.5	--	--	4.5
M9	0.3	0.2	--	--	0.2
M11	--	--	1.7	0.4	0.4
M13	1.6	0.8	--	--	0.8
M16	8.2	4.3	1.5	0.4	4.7
A1	9.7	5.1	5.3	1.3	6.4
A3	--	--	2.7	0.7	0.7
A4	--	--	0.7	0.2	0.2
A5	--	--	3.4	0.8	0.8
sum	81.4		89.3		64.5

Source: Applicant-generated table from AC-080-104 Study Report, Doc No D-18.105, Table 11-4

Percent of radioactivity of the administered dose for urine and feces was calculated with more decimal places than displayed, and these numbers were used for calculation of total (urine+feces) % radioactivity of the dose. Therefore, small differences due to rounding may appear in the tabulated summary.

¹ Calculations were based on arithmetic mean total cumulative excretion.

Agency Assessment

The C_{max} and T_{max} of aprocitentan in plasma were comparable with the concentration-time profile of ^{14}C -radioactivity; though the mean $AUC_{0-\infty}$ for aprocitentan in plasma was smaller than the $AUC_{0-\infty}$ for total ^{14}C -radioactivity in plasma (see [Table 86](#) and [Table 87](#). The primary elimination route for aprocitentan and its metabolites is through the urine (52% of the drug material), and 25% was eliminated fecally. In plasma, unchanged aprocitentan accounted for most of the radioactivity. In urine, the main products were M3, M6, M16, and A1. In feces, the main products were unchanged aprocitentan and M1. Two significant metabolic pathways are glucosidation of aprocitentan to M3 and hydrolysis to M1 and subsequent metabolites. For a discussion on the enzymes responsible for glucosidation and hydrolysis, please see [Section 14.1.2](#).

Study AC-080-105: A Single-Center, Open-Label, Single-Dose Study to Investigate the Effect of Severe Renal Impairment on the Pharmacokinetics of ACT-132577

Design

The primary objective was to investigate the PK of aprocitentan in those with severe renal impairment compared to healthy subjects. Aprocitentan 50 mg was administered in a capsule, and blood samples were obtained over 24 hours and in the mornings of Days 3, 4, 6, 8, 10, and 12 for PK analysis. 16 subjects were enrolled in two groups: Group A (8 healthy subjects), and Group B (8 subjects with severe renal function impairment). Healthy subjects were matched to renal impairment subjects based on age, sex, body weight, and height.

Results

PK was similar after a single oral dose of 50 mg in healthy subjects and subjects with severe renal impairment ([Table 89](#)). C_{max} was similar between groups, with a geometric mean ratio of 1.04 (90% confidence interval [CI] of 0.85 to 1.28) ([Table 90](#)). The T_{max} was 5 hours and 7.6 hours in healthy subjects and those with severe renal impairment, respectively. Clearance was lower in those with severe renal impairment and half-life was longer at 53.2 hours in those with severe renal impairment compared to 47.4 hours in healthy subjects. AUC_{0-t} and $AUC_{0-\infty}$ were 32% and 34% higher in those with severe renal impairment, respectively ([Table 90](#)). Plasma protein binding was similar between healthy subjects and those with severe renal impairment, ranging from 99.04% to 99.19%.

Table 89. Plasma PK Variables of Aprocitentan in Healthy Subjects and Subjects With Severe Renal Function Impairment After Administration of a Single Dose of 50 mg Aprocitentan

Parameter (unit)	Statistics	Group A (N = 8)	Group B (N = 8)
C_{max} (ng/mL)	N/missing	8/0	8/0
	Geom. mean	2840.0	2962.3
	95% CI of geom. mean	2455.3, 3285.1	2356.9, 3723.1
AUC _{0-t} (h × ng/mL)	N/missing	8/0	8/0
	Geom. mean	169029	223911
	95% CI of geom. mean	149079, 191648	187879, 266854
AUC _{0-∞} (h × ng/mL)	N/missing	8/0	8/0
	Geom. mean	170677	228252
	95% CI of geom. mean	150538, 193511	190313, 273754
$t_{1/2}$ (h)	N/missing	8/0	8/0
	Geom. mean	47.4	53.2
	95% CI of geom. mean	42.7, 52.6	47.4, 59.8
V _z /F (mL)	N/missing	8/0	8/0
	Geom. mean	20033	16827
	95% CI of geom. mean	17146, 23407	14602, 19392
CL/F (mL/h)	N/missing	8/0	8/0
	Geom. mean	293.0	219.1
	95% CI of geom. mean	258.4, 332.2	182.7, 262.7
Plasma protein binding (8 h post; %)	N/missing	8/0	8/0
	Geom. mean	99.10	99.04
	95% CI of geom. mean	99.04, 99.16	98.94, 99.14
Plasma protein binding (168 h post; %)	N/missing	8/0	8/0
	Geom. mean	99.19	99.19
	95% CI of geom. mean	99.12, 99.26	99.12, 99.26
t_{max} (h)	N/missing	8/0	8/0
	Median	5.00	7.55
	Min., Max.	4.0, 10.0	4.0, 24.0

Group of subjects: A = Healthy, B = Severe renal function impairment.

Source: Applicant generated table from AC-080-105 Study Report, Doc No D-18.125, Table 11-1.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t; CI, confidence interval; CL/F, apparent total body clearance; C_{max} , maximum concentration; geom., geometric; max, maximum; min, minimum; N, overall number of subjects; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration, V_z/F, apparent volume of distribution

Table 90. Summary of the Statistical Analyses Comparing Plasma PK Parameters of Aprocitentan Between Healthy Subjects (Group A; Reference) and Subjects With Severe Renal Function Impairment (Group B; Test)

Parameter	Statistics	ACT-132577
C_{max}	N/miss	16/0
	Ratio of geometric means (B/A)	1.0430
	90% CI of the ratio	0.8524, 1.2764
	p-value	0.7186
AUC_{0-t}	N/miss	16/0
	Ratio of geometric means (B/A)	1.3247
	90% CI of the ratio	1.1280, 1.5557
	p-value	0.0081
$AUC_{0-\infty}$	N/miss	16/0
	Ratio of geometric means (B/A)	1.3373
	90% CI of the ratio	1.1344, 1.5765
	p-value	0.0077
$t_{1/2}$	N/miss	16/0
	Ratio of geometric means (B/A)	1.1233
	90% CI of the ratio	1.0000, 1.2618
	p-value	0.1001
V_z/F	N/miss	16/0
	Ratio of geometric means (B/A)	0.8400
	90% CI of the ratio	0.7180, 0.9826
	p-value	0.0705
CL/F	N/miss	16/0
	Ratio of geometric means (B/A)	0.7478
	90% CI of the ratio	0.6343, 0.8815
	p-value	0.0076
t_{max} (h)	N/miss	16/0
	Median (B-A)	2.0500
	90% CI of the median	0.0000, 6.0000
	p-value of Wilcoxon rank-sum test	0.1641

Group of subjects: A = healthy, B = severe renal function impairment.

Source: Applicant generated table from AC-080-105 Study Report, Doc No D-18.125, Table 11-2

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t; CI, confidence interval; CL/F, apparent total body clearance; C_{max} , maximum concentration; miss, missing; N, overall number of subjects/subjects; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration, V_z/F , apparent volume of distribution

Agency Assessment

Generally, the PK of a single 50 mg dose of aprocitentan was similar between normal subjects and those with severe renal impairment. The geometric mean ratio for C_{max} was 1.04, meaning there was no clinically relevant difference between the C_{max} in those with severe renal function and healthy subjects. The AUC_{0-t} and $AUC_{0-\infty}$ were 32% and 34% higher, respectively, in those with severe renal impairment compared to those with normal renal function. Based on the results of this study, aprocitentan can be administered to those with severe renal impairment without the need for dose adjustment. This also means that those with moderate and mild renal impairment may take aprocitentan without dose adjustment.

The Applicant defined subjects with severe renal impairment as those with an eGFR between 15 mL/min/1.73 m² and 29 mL/min/1.73 m² (inclusive) and subjects with normal renal function ≥ 90 mL/min/1.73 m². Upon review, when eGFR was converted for each subject to mL/min, all subjects in the normal renal function group maintained an eGFR ≥ 90 mL/min; however, one subject in the severe renal impairment group had an eGFR >30 mL/min (35 mL/min). This minor deviation is not considered significant in the interpretation of the study results.

Study ID-080-109: An Open-Label Phase 1 Study to Investigate the Effect of Moderate Hepatic Impairment Due to Liver Cirrhosis on the Pharmacokinetics of a Single Dose of 25 mg Aprocitentan

Design

The primary objective was to investigate the PK of a single dose of 25 mg aprocitentan in subjects with moderate hepatic impairment due to liver cirrhosis compared to healthy subjects. Aprocitentan was administered as a tablet, and blood samples were drawn through 312 hours postdose. 16 subjects were enrolled in two groups: Group 1 (8 subjects with moderate hepatic impairment, Child-Pugh Grade B), and Group 2 (8 healthy subjects). Healthy subjects were matched to subjects with moderate hepatic impairment with regard to sex, age, body weight, and height.

Results

The PK of aprocitentan after a single oral dose of 25 mg was similar between those with moderate hepatic impairment and healthy subjects ([Table 91](#)). Peak plasma concentrations were reached in 4 hours in both groups. The geometric mean ratio (90% CI) for $C_{\max}$ was 1.03 (0.86-1.24) ([Table 92](#)). Clearance was lower in those with moderate hepatic impairment, and half-life was longer ([Table 91](#)). The AUC_{0-t} and $AUC_{0-\infty}$ were 22% and 23% higher, respectively, in those with moderate hepatic impairment compared to healthy subjects ([Table 92](#)). There were no differences in plasma protein binding between those with moderate hepatic impairment and healthy subjects, with mean values ranging from 98.7% to 99% ([Table 91](#)).

Table 91. Summary of PK Parameters of Aprocitentan by Group

Parameter [unit]	Statistics	Moderate hepatic impairment	Healthy
		N=8	N=8
t_{max} [h]	n/missing	8/0	8/0
	Median	4.0	4.0
	Min, Max	2, 7	2, 7
C_{max} [ng/mL]	n/missing	8/0	8/0
	Geometric mean	1307	1266
	95% CI of the geometric mean	1165, 1466	1024, 1566
AUC_{0-t} [ng*h/mL]	n/missing	8/0	8/0
	Geometric mean	97121	79758
	95% CI of the geometric mean	82383, 114495	66663, 95424
$AUC_{0-\infty}$ [ng*h/mL]	n/missing	8/0	8/0
	Geometric mean	99722	80975
	95% CI of the geometric mean	84007, 118378	67705, 96846
$t_{1/2}$ [h]	n/missing	8/0	8/0
	Geometric mean	56.4	48.3
	95% CI of the geometric mean	47.3, 67.3	42.7, 54.5
λ_z [h ⁻¹]	n/missing	8/0	8/0
	Geometric mean	0.0123	0.0144
	95% CI of the geometric mean	0.0103, 0.0147	0.0127, 0.0162
CL/F [mL/h]	n/missing	8/0	8/0
	Geometric mean	251	309
	95% CI of the geometric mean	211, 298	258, 369
V_z/F [mL]	n/missing	8/0	8/0
	Geometric mean	20396	21490
	95% CI of the geometric mean	17710, 23490	17728, 26051
PPB - 8h [%]	n/missing	8/0	8/0
	Arithmetic mean	98.7	98.9
	95% CI of the mean	98.6, 98.9	98.8, 99.0
PPB - 168h [%]	n/missing	8/0	8/0
	Arithmetic mean	98.9	99.0
	95% CI of the mean	98.7, 99.1	98.9, 99.1

Source: Applicant-generated table from ID-080-109 Study Report, Doc No D-21.217, Table 11-1
Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; CL/F, apparent total body clearance; C_{max} , maximum concentration; λ_z , first order rate constant associated with the terminal log-linear portion of the concentration-time curve; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; PPB, plasma protein binding; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration, V_z/F , apparent volume of distribution

Table 92. Summary of the Statistical Analyses Comparing Plasma PK Parameters of Aprocitentan Between Healthy Subjects and Subjects With Moderate Hepatic Impairment

t_{max} [h]	n/missing	16/0
	Median of differences (Moderate hepatic impairment - Healthy)	0.0
	90% CI of the median	-2.0, 1.0
C_{max}	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	1.032
	90% CI of the ratio	0.862, 1.236
AUC_{0-t}	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	1.218
	90% CI of the ratio	1.016, 1.460
$AUC_{0-\infty}$	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	1.232
	90% CI of the ratio	1.024, 1.481
$t_{1/2}$	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	1.169
	90% CI of the ratio	0.996, 1.372
λ_z	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	0.856
	90% CI of the ratio	0.729, 1.004
CL/F	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	0.812
	90% CI of the ratio	0.675, 0.977
V_z/F	n/missing	16/0
	Ratio of geometric means (Moderate hepatic impairment/Healthy)	0.949
	90% CI of the ratio	0.795, 1.134

Source: Applicant-generated table from ID-080-109 Study Report, Doc No D-21.217, Table 11-2

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; CL/F , apparent total body clearance; C_{max} , maximum concentration; λ_z , first order rate constant associated with the terminal log-linear portion of the concentration-time curve; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration, V_z/F , apparent volume of distribution

Agency Assessment

The PK after administration of a single 25 mg dose of aprocitentan was similar between those with moderate hepatic impairment and healthy subjects. Differences in T_{max} , C_{max} , and AUC were not clinically significant. Plasma protein binding was similar between those with moderate hepatic impairment and healthy subjects. Based on the results of this study, aprocitentan can be administered to those with moderate hepatic impairment without the need for dose adjustment. This also means that those with mild hepatic impairment may take aprocitentan without dose adjustment.

Study ID-080-107: A Single-Center, Double-Blind, Placebo-Controlled, Randomized Study to Investigate the Tolerability, Safety, and Pharmacokinetics After Multiple-Dose Administration of 25 mg Aprocitentan in Healthy Japanese and Caucasian Subjects

Design

This was a single-center, double-blind, placebo-controlled, randomized Phase 1 study in healthy Japanese and Caucasian subjects. Caucasian subjects were matched to Japanese for sex and body weight. 25 mg aprocitentan was administered in tablets orally for 10 days in the fasted condition. A total of 10 Japanese and 10 Caucasian healthy male and female subjects (1:1 sex ratio) between 20 and 45 years were included in the study. The primary objective of this study was to evaluate the relative PK characteristics of multiple-dose administration of 25 mg aprocitentan in Japanese versus Caucasian healthy subjects. The PK analysis set included 4 male and 4 female subjects that received active treatment (1 male and 1 female received placebo).

Results

The PK of aprocitentan after administration of 25 mg once daily for 10 days was similar in Japanese and Caucasian subjects. Steady state was reached between Day 7 and Day 10, with a geometric mean peak-trough fluctuation of 43.91 and 52.73% for Japanese and Caucasian subjects, respectively ([Table 93](#)). Accumulation at steady state was similar for both groups, with geometric mean accumulation index values of 2.93 and 3.05 for Japanese and Caucasian subjects, respectively ([Table 93](#)). The $C_{\max}$ geometric means ratio after the last dose was 0.94 for males, 1.1 for females, and 1.0 overall ([Table 94](#)). The $AUC_{0-\infty}$ after the last dosing interval was 0.99 for males, 1.2 for females, and 1.1 overall ([Table 94](#)).

Table 93. Summary of PK Parameters of Aprocitentan by Ethnic Group and Sex

Parameter [unit]	Statistics	Japanese			Caucasian		
		Male N = 4	Female N = 4	Total N = 8	Male N = 4	Female N = 4	Total N = 8
t_{max} (FDI) [h]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Median	3.50	3.50	3.50	3.50	3.50	3.50
	Min., Max.	3.0, 7.0	2.0, 4.0	2.0, 7.0	3.0, 8.0	3.0, 4.0	3.0, 8.0
t_{max} (LDI) [h]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Median	4.50	4.00	4.00	3.00	3.00	3.00
	Min., Max.	3.0, 6.0	2.0, 9.0	2.0, 9.0	2.0, 15.0	2.0, 4.0	2.0, 15.0
C_{max} (FDI) [ug/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	1.53	2.22	1.84	1.58	1.75	1.66
	95% CI of the geo. mean	1.27, 1.84	1.87, 2.63	1.53, 2.22	1.34, 1.85	1.39, 2.20	1.49, 1.85
C_{max} (LDI) [ug/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	4.13	5.84	4.91	4.40	5.24	4.80
	95% CI of the geo. mean	3.34, 5.10	4.87, 6.99	4.09, 5.89	3.70, 5.23	4.34, 6.31	4.27, 5.40
AUC_T (FDI) [ug*h/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	29.09	37.17	32.88	27.65	30.50	29.04
	95% CI of the geo. mean	24.01, 35.24	31.66, 43.63	28.61, 37.79	24.21, 31.58	25.39, 36.65	26.56, 31.76
AUC_T (LDI) [ug*h/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	82.25	112.87	96.35	83.30	94.07	88.52
	95% CI of the geo. mean	67.36, 100.43	96.11, 132.56	81.56, 113.83	76.61, 90.57	79.14, 111.80	81.26, 96.42
$t_{1/2}$ [h]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	48.86	49.40	49.13	47.65	49.97	48.80
	95% CI of the geo. mean	40.85, 58.44	35.65, 68.45	43.22, 55.84	42.57, 53.34	36.13, 69.12	43.28, 55.02
C_{min} [ug/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	2.65	3.71	3.14	2.62	3.09	2.84
	95% CI of the geo. mean	2.25, 3.14	3.06, 4.49	2.64, 3.73	2.24, 3.06	2.69, 3.54	2.57, 3.15
C_{avg} [ug/mL]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	3.43	4.70	4.01	3.47	3.92	3.69
	95% CI of the geo. mean	2.81, 4.18	4.00, 5.52	3.40, 4.74	3.19, 3.77	3.30, 4.66	3.39, 4.02
PTF [%]	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	42.80	45.05	43.91	51.13	54.38	52.73
	95% CI of the geo. mean	36.41, 50.32	35.87, 56.58	39.78, 48.47	41.61, 62.83	43.59, 67.84	47.35, 58.72
AI	n/missing	4/0	4/0	8/0	4/0	4/0	8/0
	Geometric mean	2.83	3.04	2.93	3.01	3.08	3.05
	95% CI of the geo. mean	2.44, 3.28	2.48, 3.72	2.67, 3.21	2.78, 3.27	2.54, 3.75	2.83, 3.28

Source: Applicant-generated table from ID-080-107 Study Report, Doc No D-19.053, Table 11-1
Abbreviations: AI, accumulation index; AUC_T , area under the concentration-time curve during a dosing interval; C_{avg} , average concentration at steady-state; CI, confidence interval; C_{max} , maximum concentration; FDI, first dosing interval; LDI, last dosing interval; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; PKS, pharmacokinetic set; PTF, peak-trough fluctuation at steady-state; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration

Table 94. Summary of the Effect of Ethnicity on the PK Parameters of Aprocitentan

Parameter [unit]	Statistics	Male N = 8	Female N = 8	Total N = 16
t_{max} (FDI) [h]	n/missing	8/0	8/0	16/0
	Median (Japanese-Caucasian)	-0.5	-0.5	0
	90% CI of the median	-5, 4	-2, 1	-1, 1
	P-value of Wilcoxon test	> 0.9999	0.8788	0.8245
t_{max} (LDI) [h]	n/missing	8/0	8/0	16/0
	Median (Japanese-Caucasian)	-4	2.5	1
	90% CI of the median	-11, 3	-2, 7	0, 2
	P-value of Wilcoxon test	0.4837	0.4551	0.2156
C_{max} (FDI) [ug/mL]	n/missing	8/0	8/0	16/0
	Ratio of geometric means (Japanese/Caucasian)	0.972	1.265	1.109
	90% CI of the ratio	0.8369, 1.1288	1.0622, 1.5070	0.9450, 1.3013
	P-value	0.7241	0.0399	0.2741
C_{max} (LDI) [ug/mL]	n/missing	8/0	8/0	16/0
	Ratio of geometric means (Japanese/Caucasian)	0.938	1.115	1.023
	90% CI of the ratio	0.7938, 1.1088	0.9511, 1.3068	0.8702, 1.2019
	P-value	0.4863	0.2318	0.8099
AUC_τ (FDI) [ug*h/mL]	n/missing	8/0	8/0	16/0
	Ratio of geometric means (Japanese/Caucasian)	1.052	1.218	1.132
	90% CI of the ratio	0.9124, 1.2131	1.0499, 1.4139	1.0009, 1.2807
	P-value	0.5147	0.0418	0.0978
AUC_τ (LDI) [ug*h/mL]	n/missing	8/0	8/0	16/0
	Ratio of geometric means (Japanese/Caucasian)	0.987	1.200	1.088
	90% CI of the ratio	0.8651, 1.1270	1.0389, 1.3859	0.9467, 1.2515
	P-value	0.8580	0.0493	0.3027

Source: Applicant-generated table from ID-080-107 Study Report, Doc No D-19.053, Table 11-2
Abbreviations: AUC_τ, area under the concentration-time curve during a dosing interval; CI, confidence interval; C_{max}, maximum concentration; FDI, first dosing interval; LDI, last dosing interval; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetic; PKS, pharmacokinetic set; t_{max}, time to reach maximum concentration

Agency Assessment

Overall, the PK of aprocitentan after multiple doses of 25 mg once daily were similar between Japanese and Caucasian healthy subjects. The geometric mean ratio values of C_{max} and AUC_τ were around 1, and 90% CIs ranged from 0.87 to 1.3 when looking at the overall data for males and females combined. Dose adjustment for ethnicity is not required for aprocitentan.

Study ID-080-103: A Single-Center, Open-Label, Two-Treatment Study to Investigate the Effect of ACT-132577 at Steady State on the Pharmacokinetics of Midazolam and its Metabolite 1-Hydroxy Midazolam in Healthy Male Subjects

Design

This study was a single-center, open-label, single-sequence, two-treatment Phase 1 study. The primary objective was to evaluate the effect of aprocitentan on the PK of midazolam and 1-hydroxy midazolam. All subjects received a single dose of 8 mg midazolam on Day 1 in the fasted condition, and a 24-hour PK profile was collected (Treatment A). Then, on Day 2, all subjects received a single dose of 150 mg aprocitentan. On Days 3, 4, and 5, a trough (predose) blood sample was collected, then 50 mg aprocitentan was administered (Treatment B1). On Day 6, a trough (predose) blood sample was collected, and a single dose of 8 mg midazolam was administered plus a single dose of 50 mg aprocitentan, and a 24-hour PK profile was collected (Treatment B2). Aprocitentan was administered in capsules.

Results

Steady state aprocitentan plasma concentrations had minimal effect on the PK of midazolam ([Table 95](#)). The geometric mean ratios (90% Cis) for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 1.14 (1.06-1.23), 1.14 (1.06-1.22), and 1.04 (0.88-1.23), respectively ([Table 96](#)). Steady-state aprocitentan plasma concentrations also had minimal effect on 1-hydroxy midazolam PK ([Table 95](#)). The geometric mean ratios (90% Cis) for AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were 0.95 (0.89-1.03), 0.98 (0.91-1.05), and 0.86 (0.70-1.05) ([Table 96](#)). Additionally, half-life for 1-hydroxy midazolam significantly increased from 5.8 to 7.7 hours ($p=0.0141$) ([Table 95](#), [Table 96](#)).

Table 95. Summary of PK Parameters of Midazolam and 1-Hydroxy Midazolam by Treatment

Parameter [unit]	Statistics	Midazolam		1-hydroxy midazolam	
		Treatment A	Treatment B2	Treatment A	Treatment B2
AUC _{0-t} [ng*h/mL]	N/miss	19/0	19/0	19/0	19/0
	Geometric mean	101.4	115.8	52.48	50.10
	95% CI of geometric mean	84.51, 121.6	94.21, 142.2	46.34, 59.44	44.99, 55.79
AUC _{0-∞} [ng*h/mL]	N/miss	19/0	19/0	19/0	19/0
	Geometric mean	103.9	118.4	54.37	53.24
	95% CI of geometric mean	86.13, 125.3	96.10, 145.8	47.92, 61.68	47.70, 59.43
C _{max} [ng/mL]	N/miss	19/0	19/0	19/0	19/0
	Geometric mean	44.20	45.98	25.55	21.91
	95% CI of geometric mean	37.70, 51.82	38.55, 54.84	20.89, 31.24	17.93, 26.77
t _{1/2} [h]	N/miss	19/0	19/0	19/0	19/0
	Geometric mean	4.177	4.199	5.793	7.672
	95% CI of geometric mean	3.411, 5.114	3.592, 4.908	4.670, 7.186	6.315, 9.322
λ _z [1/h]	N/miss	19/0	19/0	19/0	19/0
	Geometric mean	0.1660	0.1650	0.1197	0.0904
	95% CI of geometric mean	0.1356, 0.2032	0.1411, 0.1929	0.0965, 0.1485	0.0744, 0.1098
t _{max} [h]	N/miss	19/0	19/0	19/0	19/0
	Median	0.500	0.500	0.500	0.500
	Min, Max	0.33, 0.75	0.33, 2.00	0.33, 0.75	0.33, 2.00

Treatments: A = Midazolam (reference treatment), B2 = Midazolam + ACT-132577 (test treatment).

Source: Applicant-generated table from AC-080-103 Study Report, Doc No D-17.248, Table 11-1

Per-protocol set

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; C_{max}, maximum concentration; λ_z, first order rate constant associated with the terminal log-linear portion of the concentration-time curve; miss, missing; N, overall number of subjects; PK, pharmacokinetics; t_{1/2}, terminal half-life; t_{max}, time to reach maximum concentration

Table 96. Summary of Statistical Analyses of Treatment B2 to Treatment A Comparison of PK Parameters for Midazolam and 1-Hydroxy Midazolam

Parameter	Statistics	Midazolam	1-hydroxy midazolam
AUC _{0-t}	N/miss	19/0	19/0
	Ratio of geometric means (B2/A)	1.1417	0.9546
	90% CI of the ratio	1.0628, 1.2265	0.8876, 1.0268
	p-value (effect of treatment)	0.0049	0.2835
AUC _{0-∞}	N/miss	19/0	19/0
	Ratio of geometric means (B2/A)	1.1395	0.9793
	90% CI of the ratio	1.0621, 1.2227	0.9097, 1.0542
	p-value (effect of treatment)	0.0048	0.6284
C _{max}	N/miss	19/0	19/0
	Ratio of geometric means (B2/A)	1.0402	0.8576
	90% CI of the ratio	0.8784, 1.2318	0.7005, 1.0500
	p-value (effect of treatment)	0.6910	0.2047
t _½	N/miss	19/0	19/0
	Ratio of geometric means (B2/A)	1.0052	1.3244
	90% CI of the ratio	0.9295, 1.0871	1.1071, 1.5845
	p-value (effect of treatment)	0.9098	0.0141
t _{max} [h]	N/miss	19/0	19/0
	The median of difference (B2-A)	0.0000	-0.0350
	90% CI of the median	-0.0850, 0.0500	-0.0850, 0.0000
	p-value (effect of treatment)	0.7400	0.4814

Treatments: A = Midazolam (reference treatment), B2 = Midazolam + ACT-132577 (test treatment).

Source: Applicant-generated table from AC-080-103 Study Report, Doc No D-17.248, Table 11-2

Per-protocol set

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; C_{max}, maximum concentration; miss, missing; N, overall number of subjects; PK, pharmacokinetics; t_{1/2}, terminal half-life; t_{max}, time to reach maximum concentration

Agency Assessment

Steady state aprocitentan plasma concentrations did not have a clinically meaningful effect on midazolam PK, as all 90% CIs for the geometric mean ratios for AUC_{0-t}, AUC_{0-∞}, and C_{max} were within the 0.8 to 1.25 interval. Steady state aprocitentan plasma concentrations did not have any effect on AUC_{0-t} or AUC_{0-∞} of 1-hydroxy midazolam. However, the C_{max} of 1-hydroxy midazolam was reduced, and the half-life increased by about 2 hours. Overall, the results of this study indicate that aprocitentan does not alter the PK of midazolam or its metabolite to a clinically relevant extent; therefore, aprocitentan can be administered with CYP3A4 substrates without dose adjustment.

Study AC-080-106: A Single-Center, Open-Label, One-Sequence, Two-Treatment Study to Investigate the Effect of ACT-132577 at Steady State on the Pharmacokinetics of Rosuvastatin in Healthy Male Subjects

Design

This is a prospective, single-center, open-label, one-sequence, two-treatment Phase 1 study. The primary objective was to evaluate the effect of aprocitentan at steady state on the PK of a single dose of rosuvastatin in healthy male subjects. Each subject received the following treatments: Treatment A – in the morning of Day 1, a single dose of 10 mg rosuvastatin was administered in the fasted state followed by an observation period of 96 hours; Treatment B1 – doses of 25 mg aprocitentan were administered once daily from Day 5 to Day 12; and Treatment B2 – in the morning of Day 13, a single dose of 10 mg rosuvastatin was administered in the fasted state concomitantly with 25 mg aprocitentan, followed by an observation period of 120 hours. Doses of 25 mg aprocitentan were administered once daily from Day 14 to Day 17. Aprocitentan was administered as a capsule.

Results

Administration with aprocitentan increased the C_{max} of rosuvastatin by 40% (90% CI of the geometric means: 1.19-1.65) (Table 97, Table 98). The half-life decreased by 21% (90% CI of the geometric means: 0.6-1.03) (Table 97, Table 98). AUC_{0-t} and $AUC_{0-\infty}$ were not affected with geometric mean ratios of 1.07 and 0.99, respectively (Table 97, Table 98). The 90% CIs for AUC were contained within the 0.80 to 1.25 reference interval (Table 98). Mean half-life of rosuvastatin decreased from 17.9 hours to 14.1 hours, though this change was not significant ($p=0.14$) (Table 97, Table 98).

Table 97. Summary of Plasma PK Parameters of Rosuvastatin in the Presence and Absence of Aprocitentan

Parameter (unit)	Statistics	Rosuvastatin	
		Treatment A	Treatment B2
AUC _{0-t} (h*ng/mL)	N/miss	17/0	17/0
	Geometric mean	56.33	60.32
	95% CI of geometric mean	46.91, 67.65	51.16, 71.11
AUC _{0-∞} (h*ng/mL)	N/miss	17/0	17/0
	Geometric mean	63.81	63.02
	95% CI of geometric mean	52.58, 77.44	53.43, 74.32
C _{max} (ng/mL)	N/miss	17/0	17/0
	Geometric mean	5.60	7.83
	95% CI of geometric mean	4.35, 7.22	6.50, 9.42
t _{1/2} (h)	N/miss	17/0	17/0
	Geometric mean	17.850	14.067
	95% CI of geometric mean	12.389, 25.717	11.944, 16.567
t _{max} (h)	N/miss	17/0	17/0
	Median	4.50	4.50
	Min., Max.	1.5, 7.0	2.0, 5.0

Treatments: A = rosuvastatin, B2 = rosuvastatin + ACT-132577.

Source: Applicant-generated table from AC-080-106 Study Report, Doc No D-18.126, Table 11-1
 Per-protocol set

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; C_{max}, maximum plasma concentration; max, maximum; min, minimum; miss, missing; N, overall number of subjects; PK, pharmacokinetics; t_{1/2}, terminal half-life; t_{max}, time to reach maximum concentration

Table 98. Summary of the Statistical Analyses Comparing Plasma PK Parameters of Rosuvastatin in the Presence and Absence of Aprocitentan

Parameter	Statistics	Rosuvastatin
AUC _{0-t}	N/miss	17/0
	Ratio of geometric means (B2/A)	1.0707
	90% CI of the ratio	0.9441, 1.2143
	p-value (effect of treatment)	0.3571
AUC _{0-∞}	N/miss	17/0
	Ratio of geometric means (B2/A)	0.9876
	90% CI of the ratio	0.8565, 1.1388
	p-value (effect of treatment)	0.8800
C _{max}	N/miss	17/0
	Ratio of geometric means (B2/A)	1.3969
	90% CI of the ratio	1.1856, 1.6458
	p-value (effect of treatment)	0.0026
t _½	N/miss	17/0
	Ratio of geometric means (B2/A)	0.7881
	90% CI of the ratio	0.6042, 1.0278
	p-value (effect of treatment)	0.1370
t _{max} (h)	N/miss	17/0
	The median of difference B2-A	-0.7500
	90% CI of the median	-1.5000, 0.0000
	p-value (effect of treatment)	0.0742

Treatments: A = rosuvastatin, B2 = rosuvastatin + ACT-132577.

Source: Applicant-generated table from AC-080-106 Study Report, Doc No D-18.126, Table 11-2

Per-protocol set

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; C_{max}, maximum plasma concentration; miss, missing; N, overall number of subjects; PK, pharmacokinetics; t_½, terminal half-life; t_{max}, time to reach maximum concentration

Agency Assessment

In steady-state conditions, the 25 mg dose of aprocitentan did not impact the PK of rosuvastatin in a clinically relevant way. Therefore, aprocitentan can be administered with BCRP substrates without dose adjustment.

Study ID-080-110: A Single-Center, Open-Label, Randomized, Two-Way Crossover Phase 1 Study to Compare the Single-Dose Pharmacokinetics of Different Tablet Formulations of Aprocitentan in Healthy Subjects

Design

This was a prospective, open-label, randomized, two-way crossover Phase 1 study to determine the bioequivalence of aprocitentan formulations A and B. Formulation A was the reference product and had (b) (4).

Formulation B was the test product and had (b) (4).

Results

The PK of aprocitentan between the two formulations was similar. Both formulations had a $T_{\max}$ of 4 hours ([Table 99](#)). The half-life, apparent clearance, and apparent volume of distribution were also similar between both Formulation A and Formulation B ([Table 99](#)). Formulation B was bioequivalent to Formulation A, as the geometric mean ratios (90% Cis) for $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ were 0.97 (0.94-1.0), 0.97 (0.95-0.99), and 0.97 (0.94-0.99), respectively ([Table 100](#)).

Table 99. Summary of PK Parameters of Aprocitentan by Treatment

Parameter [unit] Statistics	Pharmacokinetic set N=33	
	Treatment A	Treatment B
C_{max} [ng/mL]		
n/missing	33/0	33/0
Geometric mean	1366	1329
95% CI of the geometric mean	1260, 1481	1237, 1428
AUC_{0-t} [ng·h/mL]		
n/missing	33/0	33/0
Geometric mean	81767	79052
95% CI of the geometric mean	76783, 87074	74399, 83997
AUC_{0-∞} [ng·h/mL]		
n/missing	33/0	33/0
Geometric mean	85029	82193
95% CI of the geometric mean	79863, 90530	77348, 87341
t_{max} [h]		
n/missing	33/0	33/0
Median	4.00	4.00
Min, Max	2.00, 12.00	3.00, 10.00
t_{1/2} [h]		
n/missing	33/0	33/0
Geometric mean	45.5	45.0
95% CI of the geometric mean	43.5, 47.5	42.8, 47.4
λ_z [1/h]		
n/missing	33/0	33/0
Geometric mean	0.015	0.015
95% CI of the geometric mean	0.015, 0.016	0.015, 0.016
CL/F [mL/h]		
n/missing	33/0	33/0
Geometric mean	294	304
95% CI of the geometric mean	276, 313	286, 323
V_z/F [mL]		
n/missing	33/0	33/0
Geometric mean	19283	19757
95% CI of the geometric mean	17948, 20717	18389, 21228

Treatment: A = Formulation A (reference) of 25 mg aprocitentan, B = Formulation B (test) of 25 mg aprocitentan.

Source: Applicant-generated table from ID-080-110 Study Report, Doc No D-22.208, Table 11-1

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval; CL/F, apparent total body clearance; C_{max}, maximum plasma concentration; λ_z, first order rate constant associated with the terminal log-linear portion of the concentration-time curve; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; t_{1/2}, terminal half-life; t_{max}, time to reach maximum concentration, Vz/F, apparent volume of distribution

Table 100. Effect of Treatment on PK Parameters of Aprocitentan in Plasma

Parameter [unit]	Statistics	Pharmacokinetic set N=33
C_{max}	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	0.9730
	90% CI of the ratio	0.9357, 1.0119
AUC_{0-t}	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	0.9673
	90% CI of the ratio	0.9452, 0.9900
$AUC_{0-\infty}$	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	0.9671
	90% CI of the ratio	0.9448, 0.9899
t_{max} [h]	n/missing	33/0
	Median of differences (Treatment B – Treatment A)	0.010
	90% CI of the median	0.000, 1.000
$t_{1/2}$	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	0.9897
	90% CI of the ratio	0.9721, 1.0076
λ_z	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	1.0107
	90% CI of the ratio	0.9920, 1.0298
CL/F	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	1.0340
	90% CI of the ratio	1.0100, 1.0584
V_z/F	n/missing	33/0
	Ratio of geometric means (Treatment B / Treatment A)	1.0236
	90% CI of the ratio	0.9958, 1.0522

Treatment: A = Formulation A (reference) of 25 mg aprocitentan, B = Formulation B (test) of 25 mg aprocitentan.

Source: Applicant-generated table from ID-080-110 Study Report, Doc No D-22.208, Table 11-2

Median of differences and 90% CI are calculated from the Hodges-Lehmann estimation

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; AUC_{0-t} , area under the concentration-time curve from time 0 to time t of the last measured concentration above the limit of quantification; CI, confidence interval;

CL/F, apparent total body clearance; C_{max} , maximum plasma concentration; λ_z , first order rate constant associated with the terminal log-linear portion of the concentration-time curve; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum concentration, V_z/F , apparent volume of distribution

Agency Assessment

Formulation B and A were bioequivalent, as the 90% CIs for the geometric mean ratios of the C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were all within the 80-125% bioequivalence range.

Study ID-080-108: Prospective, Single-Center, Randomized, Double-Blind, Placebo- and Moxifloxacin-Controlled, 4-Way Crossover Phase 1 Study to Assess the Effect of Multiple Therapeutic and Supratherapeutic Doses of Aprocitentan on the QT Interval Duration in Healthy Subjects

Design

This study was a prospective, single-center, randomized, double-blind, placebo- and moxifloxacin-controlled (open-label), 2-way crossover Phase 1 study. The primary objective was to demonstrate, using concentration-QT interval (QT) analysis in healthy male and female subjects, that multiple-dose administration of oral therapeutic and supratherapeutic doses of aprocitentan do not have a clinically significant effect on the QT interval. Aprocitentan was administered as 25 mg tablets. There were 4 periods in which subjects were to receive, in a randomly assigned sequence, each of the following 4 treatments: Treatment A – repeated administration of a 25 mg oral dose of aprocitentan from Day 1 to Day 10, followed by 18 days of observation; Treatment B – repeated administration of a 100 mg oral dose of aprocitentan from Day 1 to Day 10, followed by 18 days of observation; Treatment C – repeated administration of an aprocitentan-matching placebo once daily from Day 1 to Day 10, followed by 18 days of observation; and Treatment D – repeated administration of an oral dose of aprocitentan-matching placebo once daily from Day 1 to Day 9, and on Day 10, oral administration of one single 400 mg moxifloxacin tablet open-label, followed by 18 days of observation. Each of the 4 periods were separated by a minimum of 2 days.

Results

The QT results are discussed in Section [7.6.9.2](#), and the PK results for aprocitentan are discussed here. $C_{\max}$ and AUC_{τ} increased approximately dose-proportionally, and the accumulation index was about 3 ([Table 101](#)).

Table 101. PK of Aprocitentan After the First and Last Dose

Variable [unit]	Statistics	Pharmacokinetic set N=44	
		25 mg aprocitentan	100 mg aprocitentan
t_{max} (FDI) [h]	n/missing	41/3	43/1
	Median	6.00	6.00
	Min, Max	3.00, 12.00	3.00, 12.02
t_{max} (LDI) [h]	n/missing	42/2	36/8
	Median	4.00	4.00
	Min, Max	1.00, 10.00	2.00, 12.00
C_{max} (FDI) [µg/mL]	n/missing	41/3	43/1
	Geometric mean	1.27	5.53
	95% CI of the geometric mean	1.20, 1.35	4.78, 6.40
C_{max} (LDI) [µg/mL]	n/missing	42/2	36/8
	Geometric mean	3.68	16.77
	95% CI of the geometric mean	3.43, 3.95	15.52, 18.13
AUC_τ (FDI) [µg*h/mL]	n/missing	41/3	42/2
	Geometric mean	23.2	98.5
	95% CI of the geometric mean	22.0, 24.5	85.5, 113.4
AUC_τ (LDI) [µg*h/mL]	n/missing	42/2	36/8
	Geometric mean	71.6	311.8
	95% CI of the geometric mean	66.6, 76.9	290.6, 334.7
AI	n/missing	41/3	36/8
	Geometric mean	3.07	3.00
	95% CI of the geometric mean	2.94, 3.21	2.87, 3.14

Source: Applicant-generated table from ID-080-108 Study Report, Doc No D-22.079, Table 11-1

Abbreviations: AI, accumulation index; AUC_τ, area under the concentration-time curve during a dosing interval; CI, confidence interval; C_{max}, maximum plasma concentration; FDI, first dosing interval; LDI, last dosing interval; max, maximum; min, minimum; N, overall number of subjects; n, number of subjects with available value; PK, pharmacokinetics; time to reach maximum concentration

Agency Assessment

The PK of aprocitentan in Study ID-080-108 was similar to the PK in other Phase I studies conducted in healthy volunteers.

Study AC-080-102: A Single-Center, Double-Blind, Randomized, Placebo-Controlled, Two-Way Crossover Study to Evaluate Potential Body Weight Increase Induced by Fluid Retention After Administration of ACT-132577 in Healthy Male Subjects on a High-Sodium Diet

Design

This was a prospective, single-center, double-blind, randomized, placebo-controlled, two-way crossover, Phase 1 study in healthy male subjects on a high sodium diet (HSD). The primary objective was to evaluate the effect of aprocitentan on body weight in healthy male subjects on an HSD. Aprocitentan was administered in capsules.

Subjects were randomized to one of three aprocitentan dose levels and placebo and to one of two treatment sequences (A-B or B-A) in a 1:1 ratio. Treatment A received 10, 25, or 50 mg of aprocitentan once daily from Day 1 to Day 9. Subjects followed an HSD from Day -3 to Day 9. After the last dose of aprocitentan, subjects stopped the HSD and were observed for 10–12 days. Treatment B received placebo once daily from Day 1 to Day 9. Subjects were on an HSD for Day -3 to Day 9. After the last intake of placebo, subjects stopped the HSD and were observed for 10–12 days. The two treatment periods were separated by a washout of at least 7 days.

Results

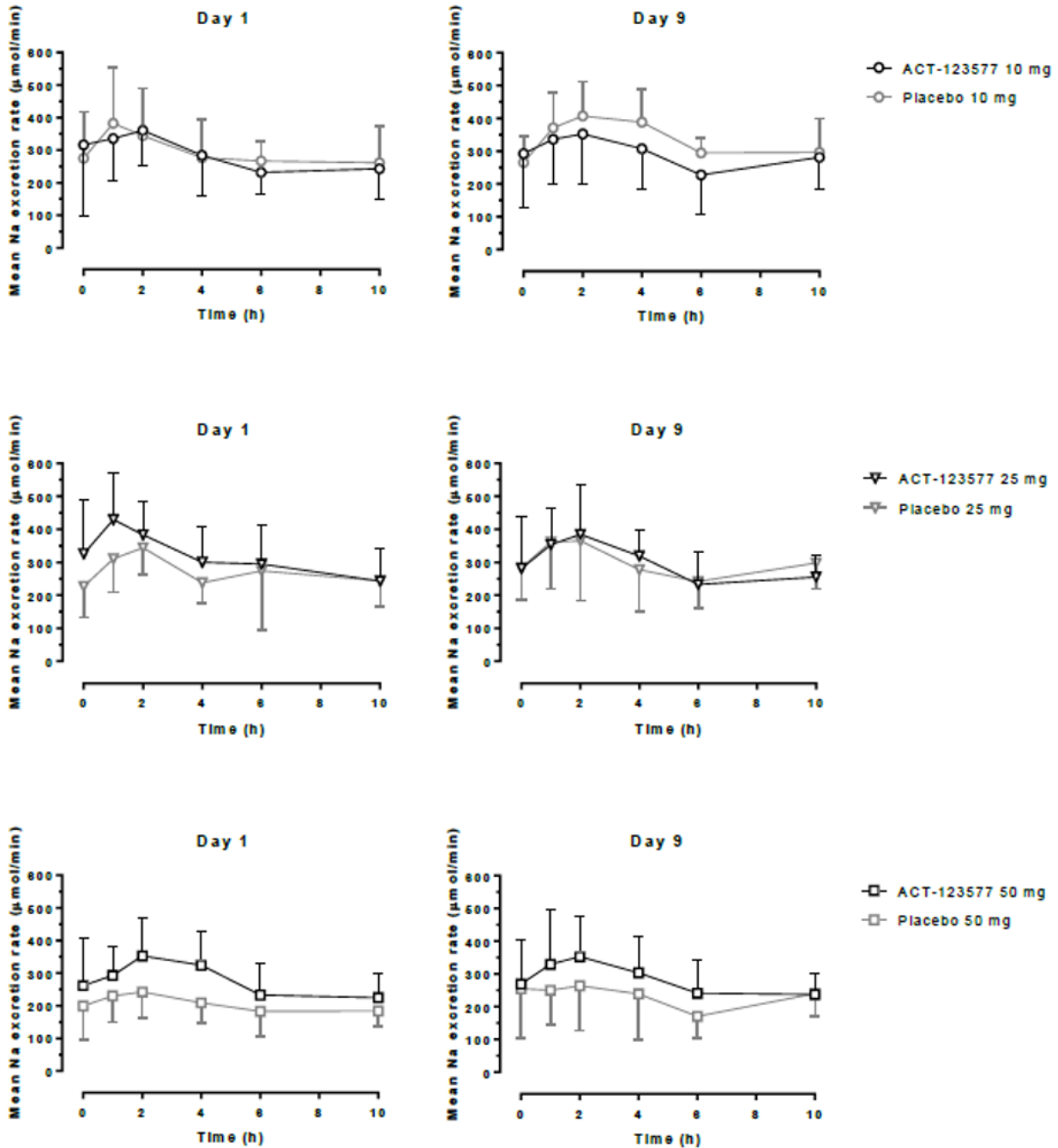
After multiple dosing for 9 days, C_{trough} increased roughly dose proportionally (mean trough concentrations of 781, 1817, and 3694 ng/mL for the 10 mg, 25 mg, and 50 mg doses, respectively).

The 10 mg aprocitentan dose was considered noninferior to placebo because the upper limit of the 90% CI did not exceed 1 kg (mean increase of +0.43 kg, CI 0.05-0.80). The 25 mg and 50 mg doses had an upper limit of the 90% CI that exceeded 1 kg, so noninferiority was not concluded (mean body weight increases of +0.77 kg, CI 0.03-1.51 and +0.83 kg, CI 0.33-1.32, respectively).

A decrease in Hb was seen in those on aprocitentan compared to placebo. Placebo-corrected differences between baseline and Day 9 were -3.1, -3.3, and -5.5 g/L for the 10 mg, 25 mg, and 50 mg doses of aprocitentan, respectively. There were slight, nondose-dependent decreases in Hct seen, as placebo-corrected differences between baseline and Day 9 were -0.5, -1, and 0 g/L for 10, 25, and 50 mg, respectively.

Aprocitentan did not affect sodium excretion parameters in a clear way, as sodium clearance, FE_{Na} , and FE_{Li} (a marker of proximal tubule sodium reabsorption) were unchanged during the 10 hour collection period on Days 1 and 9. Compared with placebo, there were small differences in sodium excretion rates during the 10 hour collection periods on Days 1 and 9. On Day 9 but not on Day 1, there was a lower sodium excretion rate with 10 mg aprocitentan than with placebo; however, this was not confirmed at the 25 mg dose level. Further, on Day 1 and Day 9, there was a consistently higher sodium excretion rate with 50 mg aprocitentan than placebo (see [Figure 17](#)).

Figure 17. Urinary Sodium Excretion Rates on Day 1 and Day 9 (Mean±SD)



Source: Applicant-generated figure from AC-080-102 Study Report, Doc No D-18.046, Figure 11-9
Abbreviations: h, hour; Na, sodium; SD, standard deviation

There were no clear patterns of changes in body fluid-regulating hormones between baseline and Day 9.

There appeared to be a small, nondose-dependent increase in extracellular water (ECW) with all three doses of aprocitentan, and there did not appear to be an increase in intracellular water.

There was no effect on systolic blood pressure (SBP), but there was a small decrease in diastolic blood pressure (DBP) between baseline and Day 9 (placebo-corrected decrease of -3.6, -4.6, and -4.8 mmHg for the 10, 25, and 50 mg aprocitentan doses, respectively) ([Table 102](#)).

Table 102. Mean Change in Vital Signs From Baseline to Day 9

Treatment	SBP / DBP	SBP	DBP
	(mmHg)	(mmHg)	(mmHg)
	Baseline	Day 9 (0 h)	Day 9 (0 h)
ACT-132577 10 mg	123.3 (± 8.46) / 63.8 (± 7.60)	-1.5 (±8.11)	-6.0 (± 7.60)
Placebo 10 mg	127.8 (± 10.53) / 61.0 (± 6.30)	-5.3 (± 12.01)	-2.4 (± 5.15)
ACT-132577 25 mg	124.8 (± 7.19) / 67.7 (± 9.21)	-1.3 (± 10.73)	-5.8 (± 2.55)
Placebo 25 mg	123.0 (± 9.92) / 64.7 (± 8.58)	0.1 (± 9.17)	-1.2 (± 6.20)
ACT-132577 50 mg	123.6 (± 7.05) / 64.1 (± 6.62)	-2.5 (± 5.50)	-3.8 (± 6.65)
Placebo 50 mg	122.4 (± 5.73) / 62.6 (± 8.18)	-2.1 (± 11.52)	1.0 (± 3.93)

Source: Applicant-generated table from AC-080-102 Study Report, Doc No D-18.046, Table 12-3

Baseline=Day 1 (0 h)

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure

Agency Assessment

The 10 mg dose is considered noninferior to placebo for body weight gain; however, noninferiority cannot be confirmed for the 25 and 50 mg doses, as the 90% CI upper limit exceeded 1 kg. While it appears that there may be some hemodilution from aprocitentan treatment while on an HSD, there was no clear dose-response relationship. There was also a nondose-dependent increase in ECW. Doses were generally well tolerated, but there was a decrease in Hb and a nondose-dependent decrease in Hct. There were also small decreases in DBP, but not SBP.

Study AC-080A201: Multi-Center, Double-Blind, Double-Dummy, Randomized, Placebo- and Active-Reference, Parallel Group, Phase 2 Dose-Finding Study With ACT-132577 in Subjects With Essential Hypertension (Grade 1 and 2)

Design

This study was a prospective, multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2, dose-finding study with aprocitentan administered in a capsule in subjects with essential hypertension (grade 1 and 2). The primary objective was to explore the dose response of aprocitentan on DBP in subjects with grade 1 or 2 essential hypertension. Secondary objectives included evaluation of the dose-response of aprocitentan on SBP, control and response rate of blood pressure, 24-hour ambulatory blood pressure monitoring (ABPM), and safety and tolerability. Other objectives included evaluation of the steady-state trough plasma concentrations of aprocitentan and possible metabolites in hypertensive subjects, evaluation of steady-state trough plasma concentrations of ET-1 in hypertensive subjects, and investigation of the correlation between ET-1 and aprocitentan plasma concentrations.

This study consisted of the following periods: prescreening, screening, run-in (Period I), treatment (Period II), withdrawal (Period III), follow-up, and end-of-study. The run-in period (Period I) was a single-blind period of 4 to 6 weeks. For antihypertensive treatment-naïve subjects, Period I lasted 4 weeks, and for subjects on antihypertensive treatment, Period I lasted 6 weeks, including a 2-week washout period for antihypertensive treatment. Period II was the double-blind treatment period of 8 weeks. Period III was the single-blind placebo period of 2 weeks where subjects were given a withdrawal placebo. 490 subjects were randomized in a 1:1:1:1:1:1 ratio into the following 6 groups: 4 aprocitentan dose groups (5, 10, 25, and 50 mg), 20 mg lisinopril, and placebo.

Results

Mean (SD) changes from baseline in mean trough sitting diastolic blood pressure (SiDBP) were -6.3 (8.9), -9.9 (8.7), -12 (8.2), and -10 (7.9) mmHg for the 5, 10, 25, and 50 mg aprocitentan dose groups respectively, -4.9 (11.1) mmHg for placebo, and -8.4 (9.6) mmHg for 20 mg lisinopril. Mean (SD) changes from baseline in mean trough sitting systolic blood pressure (SiSBP) were -10.3 (15.3), -15.0 (14.5), -18.5 (15.0) and -15.1 (11.8) mmHg in the 5, 10, 25 and 50 mg aprocitentan groups, respectively, compared with -7.7 (18.8) mmHg in the placebo group and -12.8 (16.0) mmHg in the 20 mg lisinopril group.

Mean (SD) changes from baseline to Week 8 in 24-h mean DBP were -3.76 (6.36), -6.55 (7.04), -8.86 (7.35) and -5.98 (6.63) mmHg in the 5, 10, 25 and 50 mg aprocitentan groups, respectively, compared with -2.49 (5.52) mmHg in the placebo group. The mean change from baseline for DBP in the 20 mg lisinopril group was -5.72 (9.12) mmHg. Mean (SD) changes from baseline to Week 8 in 24-h mean SBP were -3.16 (10.54), -7.72 (11.37), -9.23 (9.92) and -6.07 (8.93) mmHg in the 5, 10, 25 and 50 mg aprocitentan groups, respectively, compared with -3.54 (7.46) mmHg in the placebo group. The mean change from baseline in the 20 mg lisinopril group was -7.23 (14.33) mmHg.

Steady-state conditions were reached by Week 2 across all aprocitentan treatment groups, indicated by similar trough plasma concentrations at Weeks 2, 4, and 8.

ET-1 concentrations ranged from 1.84-1.97 pg/mL for the placebo group to 2.99-3.16 pg/mL for the 50 mg aprocitentan group.

A dose-dependent decrease in hemoglobin from baseline to Week 8 was seen for aprocitentan groups (range from -1.3 to -6.7 g/L) compared with a +2.2 g/L increase in the placebo group. There was no change in mean body weight for any aprocitentan dose group, which suggests that there may not have been significant fluid retention.

Agency Assessment

Generally, change from baseline to Week 8 in mean trough SiDBP decreased dose dependently up to 25 mg aprocitentan; however, the 50 mg dose of aprocitentan appears to have resulted in a smaller decrease in SiDBP than the 25 mg dose (-10 mmHg versus -12 mmHg, respectively). This trend was consistent with SiSBP results. Given that both the 10 mg and 50 mg aprocitentan doses appeared to decrease blood pressure to a similar extent, and the 25 mg dose appeared to have the greatest effect on blood pressure in this study, doses at or near 10 mg and 25 mg

seemed to be reasonable to explore in future studies. Two doses, a 12.5 mg and 25 mg dose, were selected for further study in the Phase 3 study (PRECISION).

Interestingly, the arithmetic mean C_{trough} values were lower (range of 1.57–1.85 $\mu\text{g}/\text{mL}$ at the different visits for the 25 mg dose; SD range of 1.27–1.43 $\mu\text{g}/\text{mL}$), with greater variability based on SD than for observations in healthy subjects (mean C_{trough} range of 2.26–3.22 $\mu\text{g}/\text{mL}$ and SD range of 0.22–0.78 $\mu\text{g}/\text{mL}$ for the 25 mg dose in healthy subjects, including Japanese subjects or subjects on a high sodium diet). There does not appear to be an explanation for this difference between subjects in this study and healthy subjects. Of note, in the Phase 3 study (PRECISION) in subjects with difficult-to-control hypertension, the mean C_{trough} (SD) values measured at Week 4 were 1.31 (0.53) $\mu\text{g}/\text{mL}$ in the aprocitentan 12.5 mg group and 2.70 (1.16) $\mu\text{g}/\text{mL}$ in the aprocitentan 25 mg group. These C_{trough} concentrations were in the range of those observed in healthy subjects at similar/equivalent doses; therefore, it is unlikely that disease state affected the C_{trough} of aprocitentan.

PRECISION: Multi-Center, Blinded, Randomized, Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension

Design

Refer to Section [6.2.1.1](#) for details on the study design.

Results

Trough plasma concentrations of aprocitentan were measured at the end of Part 1. Median plasma trough concentrations were 1310 ng/mL (range: 111–3090 ng/mL; CV%: 40.4) in the aprocitentan 12.5 mg group and 2620 ng/mL (range: 39.1–8700 ng/mL; CV%: 43.1) in the aprocitentan 25 mg group.

Changes in blood pressure from baseline to Week 4 and from baseline of the double-blind (DB)-withdrawal (WD) to Week 40 for the primary and secondary endpoints are summarized in [Table 103](#). Decreases in systolic blood pressure were similar for the 12.5 mg and 25 mg dose between baseline and Week 4. During the DB-WD, SiSBP and SiDBP continued to decrease slightly in those on 25 mg aprocitentan and increase in those on placebo.

Changes in 24 hour mean SBP and DBP from baseline to Week 4 and from the DB-WD baseline to Week 40 are in [Table 104](#). From baseline to Week 4, the 25 mg dose of aprocitentan decreased the mean 24 hour SBP and DBP more than the 12.5 mg dose. In the DB-WD period, those given placebo had increases in both 24 hour mean SBP and DBP. Changes in mean daytime and nighttime SBP and DBP from baseline to Week 4 and from the DB-WD baseline to Week 40 are in [Table 105](#). From baseline to Week 4, the 25 mg dose of aprocitentan decreased the mean daytime and nighttime SBP and DBP more than the 12.5 mg dose. During the DB-WD period, the daytime and nighttime mean SBP and DBP increased for those on placebo. While the mean nighttime SBP increased by 0.26 mmHg between the DB-WD and Week 40, likely due to variability, the increase for those on placebo was much higher (mean increase of 8.76 mmHg).

Table 103. Between-Treatment Analyses in Changes in BP (mmHg) From Baseline to Week 4 and From DB-WD Baseline to Week 40 for the Primary and the Key Secondary Endpoints

Treatment group	(DB-WD) Baseline [†] Mean (SD)	LS Mean (CL)	Difference to placebo	
			LS Mean (CL)	p-value
Change from baseline to Week 4				
SiSBP (primary efficacy endpoint)				
12.5 mg (N=243)	153.2 (8.8)	LS Mean (97.5% CL) -15.26 (-17.36, -13.17)	LS Mean (97.5% CL) -3.79 (-6.76, -0.82)	0.0042*
25 mg (N=243)	153.3 (9.0)	-15.20 (-17.27, -13.13)	-3.73 (-6.67, -0.78)	0.0046*
Placebo (N=244)	153.3 (9.0)	-11.47 (-13.57, -9.38)	-	-
SiDBP				
12.5 mg (N=243)	87.9 (9.4)	LS Mean (95% CL) -10.43 (-11.58, -9.27)	LS Mean (95% CL) -3.94 (-5.57, -2.31)	<0.0001
25 mg (N=243)	87.7 (9.7)	-10.95 (-12.09, -9.82)	-4.47 (-6.09, -2.85)	<0.0001
Placebo (N=244)	87.1 (9.9)	-6.48 (-7.63, -5.33)	-	-
Change from DB-WD baseline to Week 40				
SiSBP (key secondary endpoint)				
25 mg (N=307)	135.3 (15.6)	LS Mean (95% CL) -1.47 (-2.97, 0.04)	LS Mean (95% CL) -5.82 (-7.94, -3.71)	<0.0001**
Placebo (N=307)	136.4 (14.8)	4.36 (2.87, 5.85)	-	-
SiDBP				
25 mg (N=307)	76.1 (9.5)	LS Mean (95% CL) -0.52 (-1.54, 0.50)	LS Mean (95% CL) -5.19 (-6.62, -3.76)	<0.0001
Placebo (N=307)	76.3 (10.3)	4.67 (3.66, 5.68)	-	-

* Statistically significant at the 2.5% significance level.

** Statistically significant at the 5% significance level.

† Observed baseline values.

Mixed effects model for repeated measures: change from baseline / DB-WD baseline in SiSBP/SiDBP = baseline / DB-WD baseline SiSBP/ SiDBP + treatment + visit + treatment × visit + baseline / DB-WD baseline × visit + (for key secondary endpoint only: stratum (randomized treatment in DB part 1))

Source: Applicant-generated table from ID-080A301, Study Report, Doc No D-22.269, Table 2-1

Abbreviations: BP, blood pressure; CL, confidence limit; DB, double-blind; DB-WD, double-blind withdrawal; LS, least squares; SD, standard deviation; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 104. Between-Treatment Analyses in Changes in 24-Hour Mean SBP and DBP (mmHg) From Baseline to Week 4 and From DB-WD Baseline to Week 40

Treatment group	(DB-WD) Baseline [†] Mean (SD)	LS Mean (95% CL)	Difference to placebo	
			LS Mean (95% CL)	p-value
Change from baseline to Week 4				
24 h mean SBP				
12.5 mg (N=206)	137.65 (13.30)	-6.73 (-8.20, -5.26)	-4.18 (-6.25, -2.12)	<0.0001
25 mg (N=207)	137.62 (15.24)	-8.44 (-9.88, -7.00)	-5.90 (-7.94, -3.85)	<0.0001
Placebo (N=220)	137.10 (13.62)	-2.55 (-4.00, -1.10)	-	-
24 h mean DBP				
12.5 mg (N=206)	83.51 (8.66)	-6.25 (-7.20, -5.29)	-4.32 (-5.66, -2.98)	<0.0001
25 mg (N=207)	82.47 (10.00)	-7.74 (-8.67, -6.80)	-5.81 (-7.14, -4.49)	<0.0001
Placebo (N=220)	82.47 (9.12)	-1.92 (-2.87, -0.98)	-	-
Change from DB-WD baseline to Week 40				
24 h mean SBP				
25 mg (N=237)	129.09 (13.91)	-0.07 (-1.46, 1.32)	-6.53 (-8.50, -4.56)	<0.0001
Placebo (N=241)	128.75 (13.51)	6.46 (5.06, 7.85)	-	-
24 h mean DBP				
25 mg (N=237)	75.71 (8.68)	-0.47 (-1.34, 0.40)	-6.75 (-7.98, -5.52)	<0.0001
Placebo (N=241)	75.10 (9.00)	6.28 (5.40, 7.15)	-	-

† Observed baseline value

Source: Applicant-generated table from ID-080A301, Study Report, Doc No D-22.269, Table 2-2

Abbreviations: BP, blood pressure; CL, confidence limit; DBP, diastolic blood pressure; DB-WD, double-blind withdrawal; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SD, standard deviation

Table 105. Between-Treatment Analyses in Changes in Daytime Mean and Nighttime Mean SBP and DBP (mmHg) From Baseline to Week 4 and From DB-WD Baseline to Week 40

Treatment group	(DB-WD)	Difference to placebo		
	Baseline † Mean (SD)	LS Mean (95% CL)	LS Mean (95% CL)	p-value
Change from baseline to Week 4				
Daytime mean SBP				
12.5 mg (N=206)	141.29 (14.06)	-6.22 (-8.04, -4.39)	-3.85 (-6.42, -1.28)	0.0033
25 mg (N=207)	141.64 (16.61)	-7.72 (-9.51, -5.93)	-5.35 (-7.89, -2.81)	<0.0001
Placebo (N=220)	140.87 (15.16)	-2.37 (-4.17, -0.57)	-	-
Daytime mean DBP				
12.5 mg (N=206)	86.73 (9.69)	-6.11 (-7.28, -4.94)	-3.66 (-5.31, -2.02)	<0.0001
25 mg (N=207)	85.41 (10.54)	-8.10 (-9.24, -6.95)	-5.65 (-7.28, -4.02)	<0.0001
Placebo (N=220)	85.65 (10.64)	-2.44 (-3.60, -1.29)	-	-
Night-time mean SBP				
12.5 mg (N=206)	130.94 (15.05)	-8.14 (-10.05, -6.24)	-5.10 (-7.78, -2.41)	0.0002
25 mg (N=207)	131.61 (18.06)	-10.47 (-12.34, -8.60)	-7.42 (-10.08, -4.77)	<0.0001
Placebo (N=220)	129.99 (16.56)	-3.05 (-4.94, -1.16)	-	-
Night-time mean DBP				
12.5 mg (N=206)	77.99 (10.15)	-6.91 (-8.24, -5.58)	-4.83 (-6.70, -2.95)	<0.0001
25 mg (N=207)	77.17 (11.60)	-8.21 (-9.51, -6.91)	-6.13 (-7.98, -4.28)	<0.0001
Placebo (N=220)	76.14 (10.65)	-2.08 (-3.40, -0.77)	-	-
Change from DB-WD baseline to Week 40				
Daytime mean SBP				
25 mg (N=237)	133.36 (15.48)	-0.70 (-2.31, 0.92)	-5.93 (-8.22, -3.65)	<0.0001
Placebo (N=241)	132.78 (14.33)	5.24 (3.62, 6.85)	-	-
Daytime mean DBP				
25 mg (N=237)	78.55 (9.65)	-0.22 (-1.27, 0.82)	-5.84 (-7.32, -4.36)	<0.0001
Placebo (N=241)	78.62 (9.65)	5.62 (4.57, 6.66)	-	-
Night-time mean SBP				
25 mg (N=237)	121.62 (15.66)	0.26 (-1.47, 1.99)	-8.51 (-10.96, -6.06)	<0.0001
Placebo (N=241)	121.47 (16.38)	8.76 (7.03, 10.50)	-	-
Night-time mean DBP				
25 mg (N=237)	69.80 (9.86)	-0.73 (-1.86, 0.40)	-7.79 (-9.39, -6.19)	<0.0001
Placebo (N=241)	69.14 (10.60)	7.06 (5.93, 8.19)	-	-

† Observed baseline value

Source: Applicant-generated table from ID-080A301, Study Report, Doc No D-22.269, Table 2-3

Abbreviations: BP, blood pressure; CL, confidence limit; DBP, diastolic blood pressure; DB-WD, double-blind withdrawal; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SD, standard deviation

A subgroup analysis was conducted for African American or Black subjects (Table 106) and those with an eGFR ≥ 60 mL/min/1.73 m² (Table 107). A subgroup analysis was also conducted for those with chronic kidney disease (CKD) stage 3-4 and those aged 75 years and older (see section below on Assessment of Dose and Potential effectiveness). In African American or Black subjects, during the 4-week double-blind treatment, when corrected for placebo, SiSBP measured by uAOPBM increased in those assigned to either the 12.5 mg or 25 mg dose when corrected for placebo; however, SiDBP decreased. All ABPM measurements (24 hour mean, daytime mean, and nighttime mean) decreased compared to placebo in subjects with eGFR ≥ 60 mL/min/1.73 m², during the 4-week double-blind treatment, the SiSBP and SiDBP measured by uAOPBM decreased compared to placebo, with a greater mean decrease in those assigned to the 12.5 mg dose rather than the 25 mg dose; however, ABPM measurements (24 hour, daytime, and nighttime mean) all decreased more with the 25 mg dose compared to the 12.5 mg dose.

Table 106. Between-Treatment Analyses in Changes in BP (mmHg) From Baseline to Week 4 and From DB-WD Baseline to Week 40 for African American and Black Subjects

Variable	Difference to placebo in changes from baseline to Week 4 of DB treatment			Difference to placebo in changes from DB-WD baseline to Week 40		
	Treatment group	N	LS Mean (95% CL)	N	LS Mean (95% CL)	
		Systolic BP	Diastolic BP		Systolic BP	Diastolic BP
uAOBPM (mean trough)						
12.5 mg	27	0.63 (-7.40, 8.65)	-2.06 (-6.90, 2.78)	23	-9.87 (-16.2, -3.59)	-8.99 (-14.28, -3.70)
25 mg	28	0.12 (-7.71, 7.96)	-2.40 (-7.14, 2.34)			
ABPM						
24 h mean						
12.5 mg	22	-3.23 (-9.79, 3.33)	-1.32 (-5.77, 3.13)	21	-8.13 (-15.44, -0.82)	-7.25 (-12.24, -2.26)
25 mg	22	-7.85 (-14.34, -1.35)	-4.07 (-8.54, 0.40)			
Daytime mean						
12.5 mg	22	-6.16 (-13.36, 1.03)	-1.83 (-6.51, 2.84)	21	-3.39 (-12.95, 6.16)	-3.29 (-10.47, 3.90)
25 mg	22	-9.13 (-16.23, -2.04)	-4.81 (-9.53, -0.08)			
Night-time mean						
12.5 mg	22	-2.63 (-13.00, 7.73)	0.13 (-7.71, 7.97)	21	-9.70 (-18.63, -0.78)	-5.96 (-11.85, -0.08)
25 mg	22	-8.53 (-18.88, 1.81)	-3.47 (-11.40, 4.46)			

Source: Applicant-generated table from ID-080A301, Study Report, Doc No D-22.269, Table 2-4

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CL, confidence limit; DB, double-blind; DB-WD, double-blind withdrawal; LS, least squares; N, overall number of subjects; uAOBPM, unattended automated office blood pressure measurement

Table 107. Between-Treatment Analyses in Changes in BP (mmHg) From Baseline to Week 4 and From DB-WD Baseline to Week 40 for Subjects With eGFR $\geq$ 60 mL/min/1.73 m²

Variable	Difference to placebo in changes from baseline to Week 4 of DB treatment			Difference to placebo in changes from DB-WD baseline to Week 40		
	Treatment group	N	LS Mean (95% CL)	N	LS Mean (95% CL)	
		Systolic BP	Diastolic BP		Systolic BP	Diastolic BP
uAOBPM (mean trough)						
12.5 mg	174	-3.14 (-5.98, -0.30)	-4.00 (-5.82, -2.17)	204	-5.82 (-8.14, -3.50)	-4.87 (-6.49, -3.26)
25 mg	174	-1.26 (-4.11, 1.59)	-3.47 (-5.30, -1.64)			
ABPM						
24 h mean						
12.5 mg	161	-3.36 (-5.49, -1.23)	-4.09 (-5.51, -2.66)	180	-6.97 (-9.13, -4.81)	-6.54 (-7.93, -5.15)
25 mg	155	-4.97 (-7.13, -2.81)	-5.63 (-7.07, -4.19)			
Daytime mean						
12.5 mg	161	-2.50 (-5.19, 0.20)	-3.20 (-4.99, -1.41)	180	-6.33 (-8.78, -3.88)	-5.82 (-7.47, -4.16)
25 mg	155	-3.52 (-6.24, -0.79)	-5.37 (-7.17, -3.57)			
Night-time mean						
12.5 mg	161	-4.51 (-7.39, -1.62)	-4.80 (-6.85, -2.74)	180	-8.54 (-11.27, -5.82)	-7.45 (-9.26, -5.63)
25 mg	155	-6.61 (-9.53, -3.69)	-5.63 (-7.69, -3.56)			

Source: Applicant-generated table from ID-080A301, Study Report, Doc No D-22.2691, Table 2-5

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CL, confidence limit; DB, double-blind; DB-WD, double-blind withdrawal; LS, least squares; N, overall number of subjects; uAOBPM, unattended automated office blood pressure measurement

Agency Assessment

In the full population, the 12.5 mg and 25 mg dose showed similar SiSBP and SiDBP lowering in the first 4 weeks in the DB treatment period. ABPM parameters showed a mean greater improvement with the 25 mg dose compared to the 12.5 mg dose. The extent of the benefit of the 12.5 mg and 25 mg dose varied in different populations (i.e., different renal function status and race). In the DB-WD period, those remaining on 25 mg aprocitentan maintained lower mean blood pressure measurements compared to those who switched to placebo.

At the request of the review team, the Applicant sent in additional analysis in documents titled “Response to 4 May 2023 Information Request” (document number D-23.205), “Response to 30 May 2023 Information Request” (document number D-23.226), and “Response to 6 June 2023 Information Request” (document number D-23.234). These are discussed further in the section below on Assessment of Dose and Potential effectiveness.

Assessment of Dose and Potential Effectiveness

Per the proposed labeling, the recommended (b) (4) dose of aprocitentan is 12.5 mg orally once daily, (b) (4). The proposed dose (b) (4) based on the results of the Phase 2 and Phase 3 studies. After reviewing the data, it appears that (b) (4) the 12.5 mg (b) (4) dose provide benefit based on the primary endpoint compared to placebo; (b) (4). ABPM data suggests that there may be some improvement between the 12.5 mg and 25 mg dose; however, the improvement is minimal. Details of dose response analysis are discussed below.

In the Phase 2 study (Study AC-080A201), aprocitentan doses of 10, 25, and 50 mg decreased sitting systolic/diastolic unattended automated office blood pressure from baseline to Week 8, with placebo-corrected reductions of 7.1/4.9, 9.9/7.0 and 7.6/5.0 mmHg, respectively, compared with a reduction of 4.8/3.8 mmHg with lisinopril 20 mg. For those with valid ambulatory blood pressure readings, aprocitentan 10, 25, and 50 mg significantly decreased placebo-corrected 24-hour systolic/diastolic blood pressure by 4.0/4.0, 4.8/5.9, and 3.7/4.5 mmHg, respectively.

The doses for the Phase 3 study (PRECISION) were based on data from the Phase 2 study and the PD Phase 1 study, AC-080-102, which evaluated the effect of aprocitentan on body weight in healthy male subjects on a high-sodium diet. While noninferiority versus placebo in change from baseline to Day 9 body weight could not be demonstrated for the 25 and 50 mg doses of aprocitentan, only the 50 mg dose significantly increased body weight compared to placebo ($p=0.017$). Taken together, the Applicant selected a 12.5 mg and 25 mg once daily dose for the Phase 3 study, believing that aprocitentan in the range of 10 to 25 mg could provide the best risk/benefit profile.

In the PRECISION study, the mean ($\pm$ SE) change in SBP at 4 weeks was -15.3 ± 0.9 mmHg for aprocitentan 12.5 mg, -15.2 ± 0.9 mmHg for 25 mg, and -11.5 ± 0.9 mmHg for placebo, for a difference versus placebo of -3.8 ± 1.3 mmHg (97.5% CI: -6.8, -0.8; $p=0.004$) and -3.7 ± 1.3 mmHg (97.5% CI: -6.7, -0.8; $p=0.005$), respectively. Based on the data for the primary efficacy endpoint, it is unclear if the 25 mg dose would provide any additional benefit compared to placebo. Differences between aprocitentan 25 mg and 12.5 mg for various blood pressure endpoints are included in [Table 108](#) below. Exposure-response analyses for all blood pressure endpoints are included in [Table 109](#).

Table 108. Differences Between Aprocitentan 25 mg and 12.5 mg for Blood Pressure Endpoints

Endpoint	LS Mean change 25 mg	LS Mean change 12.5 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in mean trough SiSBP (primary endpoint)	-15.20	-15.26	0.06	-0.4
Change from baseline to Week 4 in mean trough SiDBP	-10.95	-10.43	-0.53	5.1
Change from baseline to Week 4 in 24 h mean SBP	-8.44	-6.73	-1.71	25.5
Change from baseline to Week 4 in 24 h mean DBP	-7.74	-6.25	-1.49	23.9
Change from baseline to Week 4 in daytime mean SBP	-7.72	-6.22	-1.50	24.1
Change from baseline to Week 4 in daytime mean DBP	-8.10	-6.11	-1.99	32.6
Change from baseline to Week 4 in night-time mean SBP	-10.47	-8.14	-2.33	28.6
Change from baseline to Week 4 in night-time mean DBP	-8.21	-6.91	-1.30	18.8

Source: Applicant-generated table from response to May 4, 2023 Information Request, Document Number D-23.205, Table 1

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

** Of the LS mean in the 12.5 mg group (positive values indicate a benefit for 25 mg)

N is different for each endpoint

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; LS, least squares; N, overall number of subjects; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 109. Exposure-Response Analyses for All Blood Pressure Endpoints

Exposure-response relationship	Overall population		
	R	R ²	P-value
ΔSiSBP at week 4 vs AUC _{ss}	-0.0593	0.00352	0.2305
ΔSiDBP at week 4 vs AUC _{ss}	-0.1200	0.0144	0.0152
Δ 24 h SBP at week 4 ABPM vs AUC _{ss}	-0.2441	0.0596	<.0001
Δ 24 h DBP at week 4 ABPM vs AUC _{ss}	-0.2304	0.0531	<.0001
Δ daytime SBP at week 4 ABPM vs AUC _{ss}	-0.2025	0.041	0.0002
Δ daytime DBP at week 4 ABPM vs AUC _{ss}	-0.2012	0.0405	0.0002
Δ night-time SBP at week 4 ABPM vs AUC _{ss}	-0.2249	0.0506	<.0001
Δ night-time DBP at week 4 ABPM vs AUC _{ss}	-0.1594	0.0254	0.0035

Source: Applicant-generated table from response to May 4, 2023 Information Request, Document Number D-23.205, Table 2

Abbreviations: ABPM, ambulatory blood pressure monitoring; AUC_{ss}, area under the concentration-time curve at steady-state; BP, blood pressure; Δ, change from baseline; DBP, diastolic blood pressure; R, correlation coefficient; R², coefficient of variation; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Subgroup analyses were also completed for Black or African Americans (Table 110), subjects with stage 3-4 chronic kidney disease (Table 111), the population without Black or African Americans or those with chronic kidney disease stage 3-4 (Table 112), and subjects 75 years and older (Table 113). Per the Applicant's analysis, an improvement in the primary blood pressure endpoint was seen in those with stage 3 and 4 CKD. Subgroup analyses by baseline CKD stage showed that the heterogeneity observed for CKD stages 1-2 compared to CKD stages 3-4 for the 25 mg dose was likely due to random chance (refer to subgroup analyses in Section 6.2.1.4 for details). Additionally, per the Applicant, there was a larger decrease in the primary blood pressure endpoint in the ≥75-year-old population with the 25 mg dose compared to the 12.5 mg dose.

Table 110. Differences Between Aprocitentan 25 mg and 12.5 mg for Blood Pressure Endpoints in Black or African Americans

Endpoint	LS Mean change 25 mg	LS Mean change 12.5 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in mean trough SiSBP (primary endpoint)	-11.85	-11.34	-0.50	4.4
Change from baseline to Week 4 in mean trough SiDBP	-9.56	-9.22	-0.34	3.7
Change from baseline to Week 4 in 24 h mean SBP	-8.58	-3.97	-4.62	116.4
Change from baseline to Week 4 in 24 h mean DBP	-6.78	-4.02	-2.76	68.6
Change from baseline to Week 4 in daytime mean SBP	-7.64	-4.67	-2.97	63.6
Change from baseline to Week 4 in daytime mean DBP	-7.58	-4.60	-2.97	64.6
Change from baseline to Week 4 in night-time mean SBP	-9.98	-4.08	-5.90	144.7
Change from baseline to Week 4 in night-time mean DBP	-7.23	-3.63	-3.60	99.0

Source: Applicant-generated table from response to May 4, 2023 Information Request, Document Number D-23.205, Table 3

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

** Of the LS mean in the 12.5 mg group (positive values indicate a benefit for 25 mg)

N is different for all endpoints

Abbreviations: DBP, diastolic blood pressure; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 111. Differences Between Aprocitentan 25 mg and 12.5 mg for Blood Pressure Endpoints in Chronic Kidney Disease Stage 3-4

Endpoint	LS Mean change 25 mg	LS Mean change 12.5 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in SiSBP (primary endpoint)	-19.26	-13.38	-5.88	43.9
Change from baseline to Week 4 in SiDBP	-12.25	-8.56	-3.69	43.1
Change from baseline to Week 4 in 24 h mean SBP	-10.15	-8.33	-1.82	21.8
Change from baseline to Week 4 in 24 h mean DBP	-7.95	-7.02	-0.93	13.3
Change from baseline to Week 4 in daytime mean SBP	-10.03	-6.86	-3.17	46.3
Change from baseline to Week 4 in daytime mean DBP	-7.84	-7.03	-0.82	11.7
Change from baseline to Week 4 in night-time mean SBP	-13.12	-10.66	-2.46	23.1
Change from baseline to Week 4 in night-time mean DBP	-9.53	-7.08	-2.44	34.5

Source: Applicant-generated table from response to May 4, 2023 Information Request, Document Number D-23.205, Table 4

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

** Of the LS mean in the 12.5 mg group (positive values indicate a benefit for 25 mg)

N is different for all endpoints

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 112. Differences Between Aprocitentan 25 mg and 12.5 mg Without Black or African Americans and Chronic Kidney Disease Stage 3-4 at Baseline

Endpoint	LS Mean change 12.5 mg	LS Mean change 25 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in SiSBP (primary endpoint) (FAS without Black or African American and CKD 3-4 stage at baseline)	-16.44	-14.46	1.98	-12.03
Change from baseline to Week 4 in SiDBP (FAS without Black or African American and CKD 3-4 stage at baseline)	-11.24	-10.56	0.68	-6.08
Change from baseline to Week 4 in 24 h mean SBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-6.29	-7.99	-1.69	26.88
Change from baseline to Week 4 in 24 h mean DBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-6.09	-7.83	-1.74	28.65
Change from baseline to Week 4 in daytime mean SBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-5.77	-7.14	-1.38	23.85
Change from baseline to Week 4 in daytime mean DBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-5.88	-8.26	-2.37	40.29
Change from baseline to Week 4 in nighttime mean SBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-7.43	-9.73	-2.30	31.00
Change from baseline to Week 4 in nighttime mean DBP (aFAS without Black or African American and CKD 3-4 stage at baseline)	-6.72	-7.88	-1.16	17.26

Source: Applicant-generated table from response to May 30, 2023 Information Request, Document Number D-23.226, Table 3

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

** Of the LS mean in the 12.5 mg group (positive values indicate a benefit for 25 mg)

N is different for all endpoints

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 113. Differences Between Aprocitentan 25 mg and 12.5 mg in Subjects $\geq$ 75 Years of Age at Week 4

Endpoint	LS Mean change 25 mg	LS Mean change 12.5 mg	LS Mean difference*	Percent difference**
Change from baseline to Week 4 in SiSBP (primary endpoint)	-21.12	-15.03	-6.10	40.5
Change from baseline to Week 4 in SiDBP	-14.34	-11.38	-2.96	26.0
Change from baseline to Week 4 in 24 h mean SBP	-12.45	-8.39	-4.06	48.4
Change from baseline to Week 4 in 24 h mean DBP	-8.81	-7.54	-1.27	16.8
Change from baseline to Week 4 in daytime mean SBP	-10.72	-7.43	-3.29	44.3
Change from baseline to Week 4 in daytime mean DBP	-7.53	-8.64	1.11	-12.9
Change from baseline to Week 4 in night-time mean SBP	-16.63	-11.19	-5.44	48.6
Change from baseline to Week 4 in night-time mean DBP	-10.49	-7.27	-3.22	44.3

Source: Applicant-generated table from response to October 31, 2023 Late-Cycle Meeting, Document Number D-23.379, Table 1

* Aprocitentan 25 mg-12.5 mg (negative values indicate a benefit for 25 mg)

** Of the LS mean in the 12.5 mg group (positive values indicate a benefit for 25 mg)

N is different for all endpoints

Abbreviations: DBP, diastolic blood pressure; LS, least squares; N, overall number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

In a further attempt to determine if there is any additional benefit with the 25 mg dose compared to the 12.5 mg dose, the change in blood pressure endpoints from Week 4 (end of Part 1) to Week 36 (end of Part 2) for those randomized to 12.5 mg in Part 1 was assessed ([Table 114](#)). The data at a single timepoint for the change in SiSBP for each subject from Week 4 to Week 36 is plotted in [Figure 18](#). The data in [Figure 18](#) shows that while many subjects appeared to have derived further benefit with a decrease in SiSBP from an increased aprocitentan dose, many other subjects did not.

Because SiSBP readings in the office can be variable, 24 hour mean SBP measured by ABPM may be a better measure of change in systolic blood pressure. The data for the change in 24 hour mean SBP measured by ABPM between Week 4 and Week 36 is presented in [Figure 19](#). Similar to SiSBP, there were many subjects that had a decrease in 24 hour mean SBP measured by ABPM from an increased aprocitentan dose, though many others did not. The mean difference in 24 hour SBP measured by ABPM was -0.5 mmHg, and as seen in [Figure 19](#), there are a few individuals who appear to have much larger changes in blood pressure.

Table 114. Change From Week 4 to Week 36 in Subjects Randomized to 12.5 mg in Part 1 Who Received 25 mg in Part 2

Variable	n	Week 4	Week 36	Mean difference*	Percent difference**
Mean SiSBP measured by AOBPM	150	139.51	136.81	-2.70	-1.94
Mean SiDBP measured by AOBPM	150	78.07	77.09	-0.99	-1.26
24h mean SBP measured by ABPM	134	130.00	129.48	-0.52	-0.40
24h mean DBP measured by ABPM	134	77.72	77.04	-0.68	-0.88
Daytime mean SBP measured by ABPM	134	134.60	133.94	-0.66	-0.49
Daytime mean DBP measured by ABPM	134	81.39	80.73	-0.66	-0.81
Night-time mean SBP measured by ABPM	133	121.58	121.79	0.21	0.17
Night-time mean DBP measured by ABPM	133	70.82	70.72	-0.10	-0.15

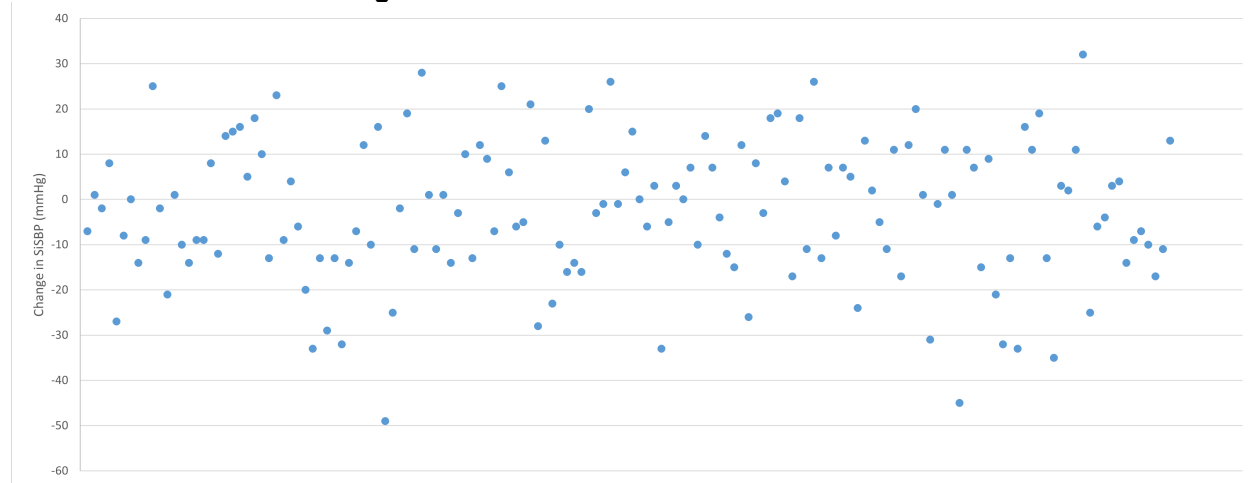
Source: Applicant-generated table from response to June 6, 2023 Information Request, Document Number D-23.232, Table 1

* Difference=Week 36-Week 4 (negative values indicating a decrease in blood pressure)

** Percent difference=Difference as a percentage of the mean at Week 4 (negative values indicating a benefit at Week 36)

Abbreviations: AOBPM, automated office blood pressure measurement; ABPM, ambulatory blood pressure monitoring; BP, blood pressure, DB, double-blind; DBP, diastolic blood pressure; n, number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

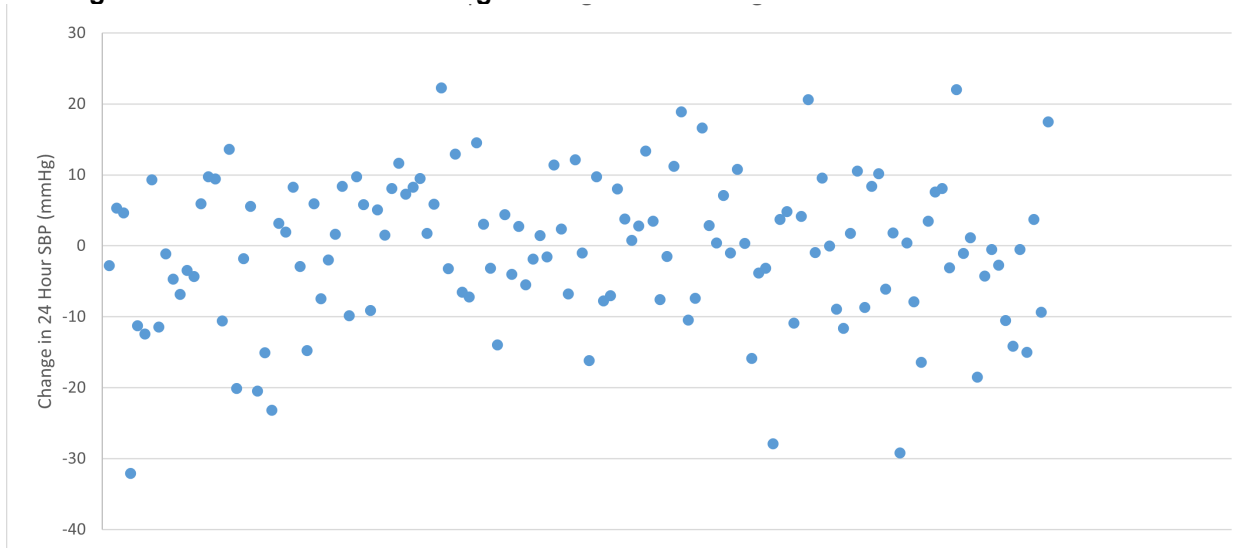
Figure 18. Plotted Change in SiSBP From Week 4 to Week 36 in Subjects Randomized to 12.5 mg in Part 1 Who Received 25 mg in Part 2



Source: Reviewer generated figure. Each point represents data from an individual subject

Abbreviation: SiSBP, sitting systolic blood pressure

Figure 19. Plotted Change in 24-Hour ABPM From Week 4 to Week 36 in Subjects Randomized to 12.5 mg in Part 1 Who Received 25 mg in Part 2



Source: Reviewer generated figure. Each point represents data from an individual subject
Abbreviations: ABPM, ambulatory blood pressure monitoring; SBP, sitting blood pressure

To evaluate if the duration of treatment alone may have an impact on BP, the change in blood pressure endpoints from Week 4 (end of Part 1) to Week 36 (end of Part 2) for those randomized to 25 mg in Part 1 (and remained on 25 mg dose in Part 2) was also assessed ([Table 115](#)). The data for the change in SiSBP for each individual from Week 4 to Week 36 is plotted in [Figure 20](#). Similar to the data in [Figure 18](#), the data in [Figure 20](#) shows that while many subjects had a decrease in SiSBP from maintaining a 25 mg aprocitentan dose, many other subjects did not. The mean difference in SiSBP was -0.84 mmHg, and as seen in [Figure 20](#), there are several individuals who appear to have much larger changes in blood pressure. Therefore, it does not appear that there was an additional large decrease in blood pressure from Week 4 to Week 36 in those receiving a 25 mg aprocitentan dose. The decrease that is seen in SiSBP could be due to variability. Similar to SiSBP, there were many subjects that had decreased 24 hour mean SBP measured by ABPM when remaining on a 25 mg dose, though many others did not. The mean difference in 24-hour SBP measured by ABPM was 1.32 mmHg, and as seen in [Figure 21](#), there are a few individuals who appear to have much larger changes in blood pressure.

Table 115. Change From Week 4 to Week 36 in Subjects Randomized to 25 mg in Part 1 Who Received 25 mg in Part 2

Variable	n	Week 4	Week 36	Mean difference*	Percent difference**
Mean SiSBP measured by AOBPM	149	137.37	136.53	-0.84	-0.61
Mean SiDBP measured by AOBPM	149	75.21	75.44	0.23	0.30
24h mean SBP measured by ABPM	137	128.62	129.94	1.32	1.03
24h mean DBP measured by ABPM	137	74.78	75.72	0.95	1.26
Daytime mean SBP measured by ABPM	137	132.97	133.81	0.83	0.63
Daytime mean DBP measured by ABPM	137	77.56	78.37	0.81	1.05
Night-time mean SBP measured by ABPM	137	120.41	123.21	2.80	2.32
Night-time mean DBP measured by ABPM	137	68.86	69.97	1.11	1.61

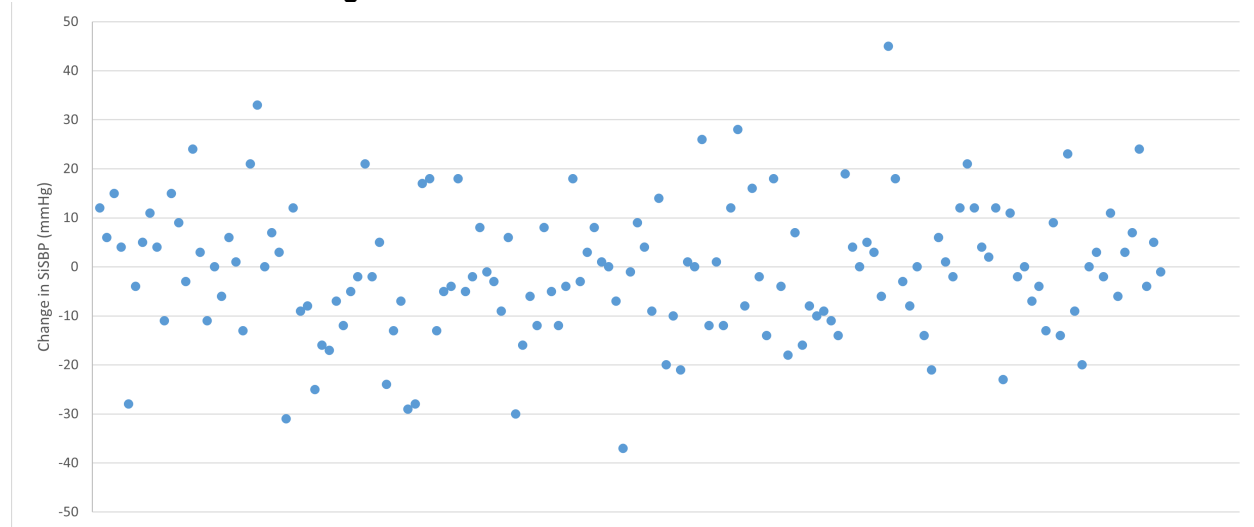
Source: Applicant-generated table from response to June 6, 2023 Information Request, Document Number D-23.232, Table 2

* Difference=Week 36-Week 4 (negative values indicating a decrease in blood pressure)

** Percent difference=Difference as a percentage of the mean at Week 4 (negative values indicating a benefit at Week 36)

Abbreviations: AOBPM, automated office blood pressure measurement; ABPM, ambulatory blood pressure monitoring; BP, blood pressure, DB, double-blind; DBP, diastolic blood pressure; n, number of subjects; SBP, systolic blood pressure; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

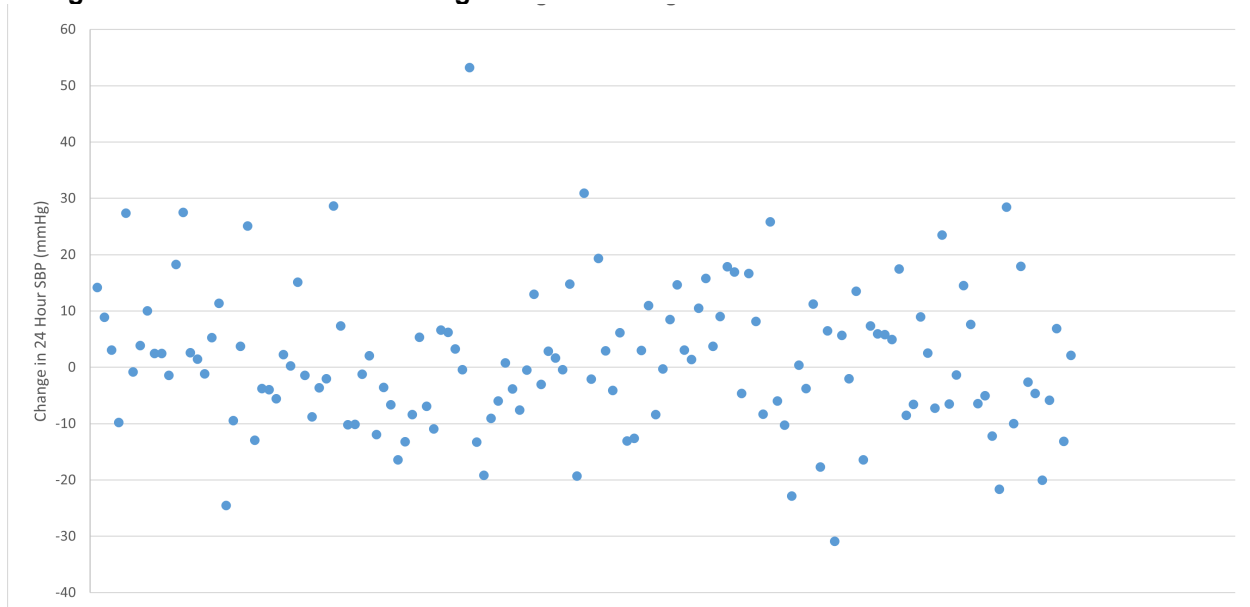
Figure 20. Plotted Change in SiSBP From Week 4 to Week 36 in Subjects Randomized to 25 mg in Part 1 Who Received 25 mg in Part 2



Source: Reviewer generated figure. Each point represents data from an individual subject.

Abbreviation: SiSBP, sitting systolic blood pressure

Figure 21. Plotted Change in 24-Hour ABPM From Week 4 to Week 36 in Subjects Randomized to 25 mg in Part 1 Who Received 25 mg in Part 2



Source: Reviewer generated figure. Each point represents data from an individual subject.
 Abbreviations: ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure

Some blood pressure endpoints (SiSBP and SiDBP) were also assessed at Week 48 after the double-blind withdrawal period and were compared to Week 4 values ([Table 116](#) and [Table 117](#)). There appears to be a greater reduction in BP in subjects who changed dose from 12.5 mg to 25 mg compared to those who stayed on the 25 mg dose; however, the differences were small. Interestingly, it appears there was a further decrease in SiSBP between Week 36 and Week 48 for those who remained on 25 mg aprocitentan.

Table 116. Mean SiSBP and SiDBP in Subjects Randomized to Receive 12.5 mg Through Week 4, 25 mg Through Week 36, and 25 mg Through Week 48

Variable	Week 4 (n = 150)	Week 36 (n = 150)	Week 48 (n = 81)
Mean SiSBP measured by AOBPM	139.51	136.81	134.20
Mean SiDBP measure dby AOBPM	78.07	77.09	76.60

Source: Derived from Applicant-generated tables from response to June 6, 2023 Information Request, Document Number D-23.232, Tables 1 and 3. BP values presented as mmHg.

Abbreviations: AOBPM, automated office blood pressure measurement; n, number of subjects; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

Table 117. Mean SiSBP and SiDBP in Subjects Randomized to Receive 25 mg Through Week 4, 25 mg Through Week 36, and 25 mg Through Week 48

Variable	Week 4 (n = 150)	Week 36 (n = 150)	Week 48 (n = 86)
Mean SiSBP measured by AOBPM	137.37	136.53	134.43
Mean SiDBP measure dby AOBPM	75.21	75.44	74.95

Source: Derived from Applicant-generated tables from response to June 6, 2023 Information Request, Document Number D-23.232, Tables 2 and 4. BP values presented as mmHg.

Abbreviations: AOBPM, automated office blood pressure measurement; n, number of subjects; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure

14.3. Bioanalytical Method Validation and Performance

Bioanalytical Method for Aprocitentan

Bioanalytical method METH-051 was developed for detecting aprocitentan in plasma via liquid chromatography with tandem mass spectrometry. A full method validation was completed, then in-study validation was conducted for each clinical study. Bioanalytical lifecycle information is included in [Table 118](#), and a summary of the method and method performance is in [Table 119](#).

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Table 118. Bioanalytical Lifecycle Information

1/3	Method validation BA-14.026	Clinical study BA-14.032 (AC-080-101)	Clinical study BA-16.014 (AC-080-102)	Clinical study BA-16.029 (AC-080-103)	Clinical study BA-16.052 (AC-080-104)	
Analyte	ACT-132577					
Internal standard	ACT-132577A (stable isotope-labeled)					
Validation type	full	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs)	
eCTD reference number	not applicable					
Method ID	METH-051					
Duration of time method in use	8 August 2014 – today					
Bioanalytical site ^a	Actelion Pharmaceuticals Ltd Gewerbstrasse 16 4123 Allschwil Switzerland			Idorsia Pharmaceuticals Ltd Hegenheimmattweg 91 4123 Allschwil Switzerland		
Matrix	plasma					
Platform	liquid chromatography/mass spectrometry (LC-MS/MS)					
Format	protein precipitation extraction					
Stock reference, lot number, expiration date ^b	Lot: ELN039-0321.1 1 st stocks prep: 30 Jun 14 expiry: 28 Oct 14 2 nd stocks prep: 21 Aug 14 expiry: 19 Dec 14 3 rd stocks prep: 5 Jan 15 ^c expiry: 3 Feb 17 4 th stocks prep: 24 Jun 15 expiry: 22 Oct 15	Lot: ELN039-0321.1 1 st stocks prep: 21 Aug 14 expiry: 19 Dec 14 2 nd stocks prep: 5 Jan 15 ^c expiry: 3 Feb 17 3 rd stocks prep: 31 Mar 15 expiry: 29 Jul 15 4 th stocks prep: 24 Jun 15 expiry: 22 Oct 15	Lot: 7 (mc) stock 001, 002 prep: 3 Nov 16 expiry: 3 Mar 17	Lot: ELN039-0321.1 prep: 12 Feb 16 ^c expiry: 13 Mar 18	Lot: 7 (mc) stock 033, 034 prep: 30 Mar 17 expiry: 28 Jul 17	
Calibration range LLOQ to ULOQ	5.00 to 10,000 ng/mL					
Matrix study population	Healthy subjects	Healthy male and female subjects	Healthy male subjects on a high-sodium diet	Healthy male subjects	Healthy male subjects	
Link to reports and applicable amendments	BA-14.026 Final Report	BA-14.032 Final Report	BA-16.014 Final Report	BA-16.029 Final Report	BA-16.052 Final Report	
Synopsis of amendment history	no amendment					
2/3	Clinical study BA-16.059 (AC-080A201)	Clinical study BA-16.061 (AC-080-105)	Clinical study BA-17.013 (AC-080-106)	Clinical study BA-18.061 (ID-080-107)	Clinical study BA-19.009 (ID-080-108)	Clinical study BA-19.099 (ID-080-109)
Analyte	ACT-132577					
Internal standard	ACT-132577A (stable isotope-labeled)					
Validation type	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs), severe renal impairment test	in-study (system suitability test, Cals and QCs), rosuvastatin interference test	in-study (system suitability test, Cals and QCs), Japanese human plasma interference test	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs), moderate hepatic impairment test
eCTD reference number	not applicable					
Method ID	METH-051					
Duration of time method in use	8 August 2014 – today					
Bioanalytical site ^a	Idorsia Pharmaceuticals Ltd Hegenheimmattweg 91 4123 Allschwil Switzerland					
Matrix	plasma					
Platform	liquid chromatography/mass spectrometry (LC-MS/MS)					
Format	protein precipitation extraction					
Stock reference, lot number, expiration date ^b	Lot: 7 (mc) stock 033, 034 prep: 30 Mar 17 expiry: 28 Jul 17	Lot: 7 (mc) stock 110, 111 prep: 7 Sep 17 expiry: 5 Jan 18	Lot: 7 (mc) stock 110, 111 prep: 7 Sep 17 expiry: 5 Jan 18	Lot: 7 (mc) stock 218, 219 prep: 20 Sep 18 expiry: 18 Jan 19	Lot: 7 (mc) stock 317, 318 prep: 12 Aug 20 expiry: 10 Dec 20 stock 365, 366 prep: 5 Aug 21 expiry: 3 Dec 21	Lot: 7 (mc) stock 295, 296 prep: 24 Feb 20 expiry: 23 Jun 20 stock 317, 318 prep: 12 Aug 20 expiry: 10 Dec 20
Calibration range LLOQ to ULOQ	5.00 to 10,000 ng/mL					
Matrix study population	Subjects with essential hypertension (grade 1 and 2)	Subjects with severe renal impairment	Healthy male subjects	Healthy Japanese and Caucasian subjects	Healthy subjects	Subjects with moderate hepatic impairment
Link to reports and applicable amendments	BA-16.059 Final Report	BA-16.061 Final Report	BA-17.013 Final Report	BA-18.061 Final Report	BA-19.009 Final Report	BA-19.099 Final Report
Synopsis of amendment history	no amendment					

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3/3	Clinical study BA-21.066 (ID-080-110)	Clinical study BA-18.001 (ID-080A301)			
Analyte	ACT-132577				
Internal standard	ACT-132577A (stable isotope-labeled)				
Validation type	in-study (system suitability test, Cals and QCs)	in-study (system suitability test, Cals and QCs)			
eCTD reference number	not applicable				
Method ID	METH-051				
Duration of time method in use	8 August 2014 – today				
Bioanalytical site ^a	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 4123 Allschwil Switzerland				
Matrix	plasma				
Platform	liquid chromatography/mass spectrometry (LC-MS/MS)				
Format	protein precipitation extraction				
Stock reference, lot number, expiration date ^b		Lot: 7 (mc) stock 271, 272 prep: 20 Sep 19 expiry: 18 Jan 20 stock 295, 296 prep: 24 Feb 20 expiry: 23 Jun 20 stock 365, 366 prep: 5 Aug 21 expiry: 3 Dec 21			
Calibration range LLOQ to ULOQ	5.00 to 10,000 ng/mL				
Matrix study population	Healthy subjects	Subjects with resistant hypertension			
Link to reports and applicable amendments	BA-21.066 Final Report	BA-18.001 Final Report			
Synopsis of amendment history	no amendment	no amendment			

Source: Applicant generated table from Summary of Method Performance, Document Number D-22.135, Table 1.

^a On June 16, 2017, the GLP bioanalytical laboratory separated from Actelion Pharmaceuticals Ltd and became part of a new company named Idorsia Pharmaceuticals Ltd. The official name and registered address of the test facility was changed to Idorsia Pharmaceuticals Ltd. Hegenheimermattweg 91, 4123 Allschwil. The test facility is the same laboratory and uses the same SOPs and equipment, and operates under the same test facility management and quality assurance team.

^b For Studies BA-14.026, BA-14.032, and BA 16.029, the stock reference is represented by the preparation date.

^c Jan 15, 2016 and Feb 12, 2016 stock solutions concentration: 1 mg/mL; all the other stock solutions were prepared at 20 mg/mL
Abbreviations: Cals, calibration standards; eCTD, electronic Common Technical Document; GLP, Good Laboratory Practice; LC/MS/MS; liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation; METH, method; prep, prepared; QCs, quality controls; ULOQ, upper limit of quantitation

Table 119. Summary of Method Performance

Bioanalytical method validation report name, amendments, and hyperlinks	BA-14.026 – Validation of an analytical method for the determination of ACT-132577 in human plasma samples by LC-MS/MS No report amendments BA-14.026 Final Report		
Method description	METH-051: Determination of ACT-132577 in human plasma samples by LC-MS/MS		
Materials used for standard calibration curve and concentration	Calibration curve prepared from working solutions prepared in acetonitrile/dimethyl sulfoxide (1:1, v/v), spiked in human plasma with a ratio of 1/50. Concentration of calibrators: 5.00, 10.0, 25.0, 100, 250, 1000, 2500, 8000 and 10,000 ng/mL		
Validated assay range	5.00 to 10,000 ng/mL		
Material used for quality controls (QCs) and concentration	Quality controls prepared from working solutions prepared in acetonitrile/dimethyl sulfoxide (1:1, v/v), spiked in human plasma with a ratio of 1/50. Concentration of quality controls: QC _{LLOQ} : 5.00 ng/mL (used in validation study only), QC _L : 10.0 ng/mL, QC _M : 250 ng/mL, QC _H : 8000 ng/mL and QC _{dil} : 50,000 ng/mL (used to test effect of dilution)		
Minimum required dilutions (MRDs)	Not applicable to this assay.		
Sources and lot of reagents	Not applicable, no critical reagents.		
Regression model and weighting	Quadratic weighted 1/x ²		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	table 4 of report BA-14.026
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0% to 3.5%	table 4 of report BA-14.026
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 6.2%	table 4 of report BA-14.026
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs (QC _{LLOQ} , QC _L , QC _M and QC _H)	-0.9% to 2.1%	table 5 of report BA-14.026
	LLOQ intra-batch accuracy (%bias)		
	LLOQ inter-batch accuracy (%bias)	-6.9% to .5%	
	QCL intra-batch accuracy (%bias)	0.3%	
	QCL inter-batch accuracy (%bias)	-1.3 to 2.9%	
	QCM intra-batch accuracy (%bias)	0.1%	
	QCM inter-batch accuracy (%bias)	-1.1 to 5.1%	
	QCH intra-batch accuracy (%bias)	2.1%	
	QCH inter-batch accuracy (%bias)	-1.6 to 0.4%	
		-0.9%	
	Inter-batch %CV	≤ 6.6%	table 5 of report BA-14.026
	LLOQ intra-batch precision (%CV)	3.5% to 4.9%	
	LLOQ inter-batch precision (%CV)	6.6%	
	QCL intra-batch precision (%CV)	2.4% to 7.1%	
QCL inter-batch precision (%CV)	4.9%		
QCM intra-batch precision (%CV)	1.3% to 4.2%		
QCM inter-batch precision (%CV)	4.0%		
QCH intra-batch precision (%CV)	1.2% to 2.0%		
QCH inter-batch precision (%CV)	1.7%		

Selectivity & matrix effect	6 lots tested. For matrix effect, bias: QCL: 5.5%; QCH: 10.1%	Bias calculated ad hoc from BA-14.026 report, table 13
Interference & specificity	6 lots tested for specificity. Any peak present at the retention time of the analyte had an area < 20% of the average area of 6 QC _{LLOQ} samples. Any peak present at the retention time of the internal standard had an area < 5% of the average area of 6 QC _{LLOQ} samples <u>Plasma arising from subjects with severe renal impairment interference test (6 pooled subjects)</u> Bias: QCL: -3.9%; QC _M : 0.4%; QCH: 0.4% No effect on quantification <u>Rosuvastatin Interference test (50.0 ng/mL)</u> Bias: QCL: 10.3%; QC _M : 10.0%; QCH: 1.6% No effect on quantification <u>Plasma arising from Japanese healthy subjects interference test (10 pooled subjects)</u> Bias: QCL: 0.3%; QC _M : 4.1%; QCH: 10.6% No effect on quantification <u>Plasma arising from subjects with moderate hepatic impairment (6 pooled subjects)</u> Bias: QCL: 3.2%; QC _M : 4.1%; QCH: 1.4% No effect on quantification	table 3 of report BA-14.026 table 4 of report BA-16.061 table 4 of report BA-17.013 table 4 of report BA-18.061 table 5 of report BA-19.099
Hemolysis effect	bias: QCL: 8.8%; QCH: 13.3%	Bias calculated ad hoc from BA-14.026 report, table 13
Lipemic effect	bias: QCL: 3.9%; QCH: 11.6%	Bias calculated ad hoc from BA-14.026 report, table 13
Dilution linearity & hook effect	Tested concentration: 50,000 ng/mL. Dilution factor: 10; Bias: -5.8%	table 15 of report BA-14.026
Bench-top/process stability^a	Bench-top stability: 24 h at room temperature in human plasma Process stability: 67 h at 4 °C in sample extracts	3.00 ng/mL: table 31 of report amendment 1 SBA_S_04081 QCH: table 8 of report BA-14.026 and table 10 of report BA-14.026
Re-injection reproducibility	38 h at 4 °C	table 11 of report BA-14.026
Freeze-Thaw stability^a	3 cycles at nominally -20 °C	3.00 ng/mL: table 11 of report SBA_S_04081 QCH: table 7 of report BA-14.026

	3 cycles at nominally -80 °C	table 7 of report BA-14.026
Long-term storage^a	385 days at -20 °C and -80 °C	3.00 ng/mL at -25 °C: table 28 of report amendment 1 SBA_S_04081 table 9 of report BA-14.026
Stability in solution	20 mg/mL stock solution: 120 days at -80 °C 1 mg/mL stock solution: 760 days at -80 °C and 16 h at room temperature 100 ng/mL and 80,000 ng/mL working solutions: 110 days at -80 °C 25.0 µg/mL and 8000 µg/mL working solutions: 131 days at -80 °C	table 32 of report BA-13.229 table 33 of report BA-13.229
Recovery	QCL: 86.1%; QCM: 95.6%; QCH: 101.0 % %CV: 8.0%	table 14 of report BA-14.026
Average recovery of drug (% mean)	94.2%	Calculated ad hoc from table 14 of report BA-14.026
Maximum number of samples within one batch	150 study samples	table 6 of report BA-14.026
Parallelism	Not applicable	
Carry over	2 double blank samples (no reference item and no internal standard) to be interspersed after the injection of a high concentration sample or before a low concentration sample	table 16 of report BA-14.026

Source: Applicant-generated table from Summary of Method Performance, Document Number D-22.135, Table 2

^a Stability data covering QCL level for the freeze-and-thaw and long-term stability at -20°C as well as short-term stability at room temperature were obtained as part of study SBA_S_04081.

Abbreviations: CV, coefficient of variation; h, hour; LC/MS/MS; liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantitation; MRD, minimum required dilution; QC_{dil}, quality control dilution; QC_H, quality control high; QC_L, quality control low; QC_{LLOQ}, quality control lower limit of quantification; QC_M, quality control medium; QCs, quality controls; ULOQ, upper limit of quantitation; v/v, volume per volume

Method performance was assessed with each study and are considered acceptable.

Bioanalytical Method for Midazolam

A method for determining midazolam and 1-hydroxy midazolam in plasma samples was developed and validated by (b) (4) Project-No.: 079B16-Val).

Results of the validation are presented in [Table 120](#) for midazolam and [Table 121](#) for 1-hydroxymidazolam. The assay is adequately validated, and long-term stability in plasma was documented out to 135 days and 181 days at ≤ -70 °C and ≤ -20 °C, respectively.

Table 120. Summary of Validation Data for Midazolam

Parameters	Results		Acceptance criteria
Selectivity for midazolam			
Investigation of interference caused by blank plasma (six different plasma sources)	No interference		The chromatograms should show no interfering peak at retention time of midazolam. If there is a peak present, the area should be < 20 % of the mean peak area of midazolam at LLOQ.
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma caused no interfering peak		
Investigation of interference caused by further analytes, metabolites and internal standards	Both internal standards caused no interfering peak; 1-hydroxymidazolam and 4-hydroxymidazolam showed less than 20 % interference compared to response of LLOQ		Acceptance criteria were fulfilled
Investigation of interference caused by co-medication	Co-medication caused no interfering peak		
Selectivity for internal standard midazolam-d₄			
Investigation of interference caused by blank plasma (six different plasma sources)	No interference		The chromatograms should show no interfering peak at retention time of midazolam-d ₄ . If there is a peak present, the area should be < 5 % of the mean peak area of the internal standard in LLOQ samples.
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma caused no interfering peak		
Investigation of interference caused by the analytes, metabolites and further internal standard	1-Hydroxymidazolam, 1-hydroxymidazolam-d ₄ and 4-hydroxymidazolam caused no interfering peak; midazolam showed less than 5 % interference compared to response of internal standard in LLOQ samples		Acceptance criteria were fulfilled
Investigation of interference caused by co-medication	Co-medication caused no interfering peak		
Carryover	Response in blank samples after ULOQ showed less than 20 % interference at retention time of midazolam and less than 5 % interference at retention time of its internal standard compared to the respective response in LLOQ samples.		Any carryover from a sample at the ULOQ should represent a response that is not greater than 20 % of the mean peak area found for midazolam and not greater than 5 % of the mean peak area found for its internal standard in LLOQ samples. Acceptance criteria were fulfilled
Matrix effect (CV %)	75.0 ng/ml	0.250 ng/ml	CV of the IS normalised matrix factors should be maximally 15 %.
Six different plasma sources	10.0 %	6.8 %	Acceptance criteria were fulfilled
Influence of haemolysed plasma	4.8 %	5.9 %	
Influence of hyperlipidaemic plasma	5.6 %	4.1 %	

Parameters		Results	Acceptance criteria
Linearity		0.1000 ng/ml – 100.0 ng/ml Linearity could be demonstrated	RD of calculated concentrations from the nominal values should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 75 % (in the actual method validation at least seven) of the non-zero standard points should fulfil the acceptance criteria. Acceptance criteria were fulfilled
Lower limit of quantification		LLOQ: 0.1000 ng/ml Could be determined with acceptable precision and accuracy	
Precision (CV %)	within-run	1.4 - 2.3 % (75.0 ng/ml)	<i>Within-run and between-run:</i> CV should be maximally 15 % (LLOQ: 20 %). Acceptance criteria were fulfilled
		1.7 - 3.7 % (30.0 ng/ml)	
		1.8 - 2.8 % (0.250 ng/ml)	
		2.7 - 6.8 % (0.1000 ng/ml)	
	between-run	3.5 % (75.0 ng/ml)	
		3.4 % (30.0 ng/ml)	
		3.4 % (0.250 ng/ml)	
		5.6 % (0.10000 ng/ml)	
dilution (1:10)	3.3 % (50.0 ng/ml)		
Influence of different individual matrix	4.3 % (75.0 ng/ml)		
	2.0 % (0.250 ng/ml)		
Influence of haemolysis	1.4 % (75.0 ng/ml)		
	1.2 % (0.250 ng/ml)		
Influence of hyperlipidaemic plasma	2.6 % (75.0 ng/ml)		
	2.9 % (0.250 ng/ml)		
Accuracy ($\pm$ RD %)	within-run	-1.6 - 4.7 % (75.0 ng/ml)	<i>Within-run:</i> RD of the calculated concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 67 % of the QC samples at each concentration should fulfil the acceptance criteria. Additionally RD of the mean concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). <i>Between-run:</i> Calculated mean concentration from three different runs should deviate not more than $\pm 15\%$ (LLOQ: $\pm 20\%$) from the nominal value. Acceptance criteria were fulfilled
		-3.0 - 0.7 % (30.0 ng/ml)	
		-0.8 - 4.8 % (0.250 ng/ml)	
		-2.2 - 4.3 % (0.1000 ng/ml)	
	between-run	0.5 % (75.0 ng/ml)	
		-1.7 % (30.0 ng/ml)	
		1.6 % (0.250 ng/ml)	
		0.2 % (0.10000 ng/ml)	
dilution (1:10)	-1.4 % (50.0 ng/ml)		
Influence of different individual matrix	3.7 % (75.0 ng/ml)		
	4.8 % (0.250 ng/ml)		
Influence of haemolysis	2.1 % (75.0 ng/ml)		
	3.2 % (0.250 ng/ml)		
Influence of hyperlipidaemic plasma	1.6 % (75.0 ng/ml)		
	2.0 % (0.250 ng/ml)		

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Parameters		Results		Acceptance criteria
Recovery rate		92.4 %	(75.0 ng/ml)	CV should be maximally 15 % over the three analyte concentrations. Acceptance criteria were fulfilled
		92.2 %	(30.0 ng/ml)	
		96.4 %	(0.250 ng/ml)	
		CV = 2.5 %		
IS:		93.3 %	(5.00 ng/ml)	
Stability				
Plasma	stored at ≤ -20 °C	75.0 ng/ml	0.250 ng/ml	Mean concentration of the stability samples (stored samples) at each QC level should be within ± 15 % of the nominal concentration (stability results should be within 85 % - 115 %). Acceptance criteria were fulfilled
	up to 4 days	101.9 %	100.8 %	
	up to 87 days	94.8 %	103.6 %	
	stored at ≤ -70 °C	75.0 ng/ml	0.250 ng/ml	
	up to 4 days	103.1 %	103.2 %	
	up to 87 days	94.7 %	101.6 %	
	freeze/thaw cycles:	75.0 ng/ml	0.250 ng/ml	
	1 st cycle	101.5 %	102.8 %	
	2 nd cycle	101.6 %	102.0 %	
	3 rd cycle	103.1 %	97.6 %	
stored at RT:	75.0 ng/ml	0.250 ng/ml		
6 h	102.0 %	99.6 %		
Final extract	stored for	75.0 ng/ml	0.250 ng/ml	
	72 h in the AS	97.7 %	99.2 %	

Source: Table generated by (b) (4) Project-No.: 079B16-Val, Table 1a
 Abbreviations: AS, autosampler; CV, coefficient of variation; IS, internal standard; LLOQ, lower limit of quantitation; QC, quality control; ULOQ, upper limit of quantitation

Table 121. Summary of Validation Data for 1-Hydroxymidazolam

Parameters	Results		Acceptance criteria
Selectivity for 1-hydroxymidazolam			
Investigation of interference caused by blank plasma (six different plasma sources)	No interference		The chromatograms should show no interfering peak at the retention time of 1-hydroxymidazolam. If there is a peak present, the area should be < 20 % of the mean peak area of 1-hydroxymidazolam at LLOQ. Acceptance criteria were fulfilled
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma caused no interfering peak		
Investigation of interference caused by analytes, metabolites and internal standards	Both internal standards, midazolam and 4-hydroxymidazolam caused no interfering peak		
Investigation of interference caused by co-medication	Co-medication caused no interfering peak		
Selectivity for internal standard 1-hydroxymidazolam-d₄			
Investigation of interference caused by blank plasma (six different plasma sources)	No interference		The chromatograms should show no interfering peak at the retention time of 1-hydroxymidazolam. If there is a peak present, the area should be < 5 % of the mean peak area of the internal standard in LLOQ samples. Acceptance criteria were fulfilled
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma caused no interfering peak		
Investigation of interference caused by analyte, metabolites and internal standard	Midazolam-d ₄ , midazolam, 1-hydroxymidazolam and 4-hydroxymidazolam caused no interfering peak		
Investigation of interference caused by co-medication	Co-medication caused no interfering peak		
Carryover	Response in blank samples after ULOQ showed less than 20 % interference at retention time of 1-hydroxymidazolam and less than 5 % interference at retention time of its internal standard compared to the respective response in LLOQ samples.		Any carryover from a sample at the ULOQ should represent a response that is not greater than 20 % of the mean peak area found for 1-hydroxymidazolam and not greater than 5 % of the mean peak area found for its internal standard in LLOQ samples. Acceptance criteria were fulfilled
Matrix effect (CV %)			CV of the IS normalised matrix factors should be maximally 15 %. Acceptance criteria were fulfilled
Six different plasma sources	75.0 ng/ml	0.250 ng/ml	
Influence of haemolysed plasma	5.2 %	6.3 %	
Influence of hyperlipidaemic plasma	3.7 %	6.3 %	
	2.4 %	4.3 %	

Parameters		Results	Acceptance criteria	
Linearity		0.1000 ng/ml – 100.0 ng/ml Linearity could be demonstrated	RD of calculated concentrations from the nominal values should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 75 % (in the actual method validation at least seven) of the non-zero standard points should fulfil the acceptance criteria. Acceptance criteria were fulfilled	
Lower limit of quantification		LLOQ: 0.1000 ng/ml Could be determined with acceptable precision and accuracy		
Precision (CV %)	within-run	1.3 - 2.9 % (75.0 ng/ml)	<i>Within-run and between-run:</i> CV should be maximally 15 % (LLOQ: 20 %). Acceptance criteria were fulfilled	
		1.5 - 2.6 % (30.0 ng/ml)		
		2.5 - 3.9 % (0.250 ng/ml)		
		3.9 - 6.1 % (0.1000 ng/ml)		
between-run	2.7 % (75.0 ng/ml)			
	2.8 % (30.0 ng/ml)			
	4.4 % (0.250 ng/ml)			
	5.0 % (0.10000 ng/ml)			
dilution (1:10)	2.8 % (50.0 ng/ml)			
Precision (CV %)	Influence of different individual matrix	2.2 % (75.0 ng/ml) 4.2 % (0.250 ng/ml)		CV should be maximally 15 % (LLOQ: 20 %). Acceptance criteria were fulfilled
	Influence of haemolysis	0.8 % (75.0 ng/ml) 4.3 % (0.250 ng/ml)		
	Influence of hyperlipidaemic plasma	1.9 % (75.0 ng/ml) 1.3 % (0.250 ng/ml)		
Accuracy ($\pm$ RD %)	within-run	-4.4 - -1.1 % (75.0 ng/ml)	<i>Within-run:</i> RD of the calculated concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 67 % of the QC samples at each concentration should fulfil the acceptance criteria. Additionally RD of the mean concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). <i>Between-run:</i> Calculated mean concentration from three different runs should deviate not more than $\pm 15\%$ (LLOQ: $\pm 20\%$) from the nominal value. Acceptance criteria were fulfilled	
		0.3 - 5.3 % (30.0 ng/ml)		
		-7.6 - -0.4 % (0.250 ng/ml)		
		-7.4 - -4.1 % (0.1000 ng/ml)		
	between-run	-3.3 % (75.0 ng/ml)		
		3.0 % (30.0 ng/ml)		
		-4.4 % (0.250 ng/ml)		
		-6.2 % (0.10000 ng/ml)		
	dilution (1:10)	1.4 % (50.0 ng/ml)		
	Influence of different individual matrix	0.1 % (75.0 ng/ml) 2.4 % (0.250 ng/ml)		
Influence of haemolysis	0.0 % (75.0 ng/ml) 2.0 % (0.250 ng/ml)			
Influence of hyperlipidaemic plasma	0.9 % (75.0 ng/ml) -0.4 % (0.250 ng/ml)			

Parameters		Results		Acceptance criteria
Recovery rate		93.6 %	(75.0 ng/ml)	CV should be maximally 15 % over the three analyte concentrations. Acceptance criteria were fulfilled
		96.6 %	(30.0 ng/ml)	
		100.2 %	(0.250 ng/ml)	
		CV = 3.4 %		
IS:		91.9 %	(10.00 ng/ml)	
Stability				
Plasma	stored at ≤ -20 °C	75.0 ng/ml	0.250 ng/ml	Mean concentration of the stability samples (stored samples) at each QC level should be within ± 15 % of the nominal concentration (stability results should be within 85 % - 115 %). Acceptance criteria were fulfilled
	up to 4 days	100.7 %	103.2 %	
	up to 87 days	100.5 %	104.8 %	
	stored at ≤ -70 °C	75.0 ng/ml	0.250 ng/ml	
	up to 4 days	100.8 %	101.6 %	
	up to 87 days	99.2 %	102.8 %	
	freeze/thaw cycles:	75.0 ng/ml	0.250 ng/ml	
	1 st cycle	103.3 %	99.2 %	
	2 nd cycle	104.1 %	98.8 %	
	3 rd cycle	99.3 %	101.2 %	
stored at RT:	75.0 ng/ml	0.250 ng/ml		
6 h	98.9 %	99.2 %		
Final extract	stored for	75.0 ng/ml	0.250 ng/ml	
	72 h in the AS	103.5 %	102.0 %	

Source: Table generated by (b) (4) Project-No.: 079B16-Val, Table 1b
Abbreviations: AS, autosampler; CV, coefficient of variation; h, hour; IS, internal standard; LLOQ, lower limit of quantitation; QC, quality control; RD, relative deviation; ULOQ, upper limit of quantitation

Bioanalytical Method for Rosuvastatin

A method for determining rosuvastatin in plasma samples was developed and validated by (b) (4) Project-No: 307B17-Val). Results of the validation are presented in [Table 122](#). The assay is adequately validated, and long-term stability in plasma was documented out to 254 days and 187 days at ≤ -70 °C for QC-H (37.5 ng/mL) and QC-L (0.1000 ng/mL), respectively.

Table 122. Summary of Validation Data for Rosuvastatin

Parameters	Results		Acceptance criteria
Selectivity for rosuvastatin			
Investigation of interference caused by blank plasma (six different plasma sources)	Response in blank samples showed less than 20 % interference compared to response of rosuvastatin at LLOQ		The chromatograms should show no interfering peak at the retention time of rosuvastatin. If there is a peak present, the area should be < 20 % of the mean peak area of rosuvastatin at LLOQ. Acceptance criteria were fulfilled
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma showed less than 20 % interference compared to response of rosuvastatin at LLOQ		
Investigation of interference caused by internal standard	Internal standard showed less than 20 % interference compared to response of rosuvastatin at LLOQ		
Investigation of interference caused by metabolite rosuvastatin lactone	Metabolite showed more than 20 % interference compared to response of rosuvastatin at LLOQ (explanation see chapter 12.2.2)		
Investigation of interference caused by co-medication	Co-medication showed less than 20 % interference compared to response of rosuvastatin at of LLOQ		
Selectivity for internal standard			
Investigation of interference caused by blank plasma (six different plasma sources)	No interference		The chromatograms should show no interfering peak at the retention time of internal standard. If there is a peak present, the area should be < 5 % of the mean peak area of internal standard in LLOQ samples. Acceptance criteria were fulfilled
Investigation of interference caused by haemolysed blank plasma and hyperlipidaemic blank plasma	Haemolysed blank plasma and hyperlipidaemic blank plasma caused no interfering peak		
Investigation of interference caused by rosuvastatin	Rosuvastatin caused no interfering peak		
Investigation of interference caused by metabolite rosuvastatin lactone	Metabolite caused no interfering peak		
Investigation of interference caused by co-medication	Co-medication caused no interfering peak		
Carryover	No carryover		Any carryover from a sample at the ULOQ should represent a response that is not greater than 20 % of the mean peak area found for rosuvastatin and not greater than 5 % of the mean peak area found for internal standard in LLOQ samples. Acceptance criteria were fulfilled
Matrix effect (CV %)	37.5 ng/ml	0.250 ng/ml	CV of the IS normalised matrix factors should be maximally 15 %. Acceptance criteria were fulfilled
Six different plasma sources	2.7 %	1.7 %	
Influence of haemolysed plasma	2.5 %	8.8 %	
Influence of hyperlipidaemic plasma	1.6 %	3.1 %	

Parameters		Results	Acceptance criteria
Linearity		0.1000 ng/ml – 50.0 ng/ml Linearity could be demonstrated	RD of calculated concentrations from the nominal values should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 75 % (in the actual method validation at least eight) of the non-zero standard points should fulfil the acceptance criteria. Acceptance criteria were fulfilled
Lower limit of quantification		LLOQ: 0.1000 ng/ml Could be determined with acceptable precision and accuracy	
Precision (CV %)	within-run	0.7 – 3.4 % (37.5 ng/ml)	<i>Within-run and between-run:</i> CV should be maximally 15 % (LLOQ: 20 %). Acceptance criteria were fulfilled
		1.6 – 3.2 % (15.0 ng/ml)	
		1.6 – 2.7 % (0.250 ng/ml)	
		3.7 – 10.2 % (0.1000 ng/ml)	
	between-run	3.6 % (37.5 ng/ml)	
		3.0 % (15.0 ng/ml)	
		2.5 % (0.250 ng/ml)	
		8.6 % (0.1000 ng/ml)	
dilution (1:10)	1.2 % (20.0 ng/ml)		
Influence of different individual matrix	1.7 % (37.5 ng/ml)		
	2.5 % (0.250 ng/ml)		
Influence of haemolysis	1.2 % (37.5 ng/ml)		
	4.0 % (0.250 ng/ml)		
Influence of hyperlipidaemic plasma	0.6 % (37.5 ng/ml)		
	2.9 % (0.250 ng/ml)		
Accuracy ($\pm$ RD %)	within-run	-4.5 – 2.4 % (37.5 ng/ml)	<i>Within-run:</i> RD of the calculated concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). 67 % of the QC samples at each concentration should fulfil the acceptance criteria. Additionally RD of the mean concentration from the nominal value should be maximally $\pm 15\%$ (LLOQ: $\pm 20\%$). <i>Between-run:</i> Calculated mean concentration from three different runs should deviate not more than $\pm 15\%$ (LLOQ: $\pm 20\%$) from the nominal value. Acceptance criteria were fulfilled
		-0.7 – 3.3 % (15.0 ng/ml)	
		-0.8 – 2.4 % (0.250 ng/ml)	
		-2.0 – 12.1 % (0.1000 ng/ml)	
	between-run	-1.3 % (37.5 ng/ml)	
		1.3 % (15.0 ng/ml)	
		1.2 % (0.250 ng/ml)	
		3.8 % (0.1000 ng/ml)	
dilution (1:10)	-8.5 % (20.0 ng/ml)		
Influence of different individual matrix	-0.3 % (37.5 ng/ml)		
	-0.4 % (0.250 ng/ml)		
Influence of haemolysis	0.8 % (37.5 ng/ml)		
	-2.8 % (0.250 ng/ml)		
Influence of hyperlipidaemic plasma	0.5 % (37.5 ng/ml)		
	-3.2 % (0.250 ng/ml)		

Parameters		Results		Acceptance criteria
Recovery rate		95.0 %	(37.5 ng/ml)	CV should be maximally 15 % over the three analyte concentrations. Acceptance criteria were fulfilled
		93.4 %	(15.0 ng/ml)	
		94.0 %	(0.250 ng/ml)	
		CV = 0.9 %		
		IS:	97.7 %	(10.00 ng/ml)
Stability				
Plasma	stored at ≤ -70 °C	37.5 ng/ml	0.250 ng/ml	Mean concentration of the stability samples (stored samples) at each QC level should be within ± 15 % of the nominal concentration (stability results should be within 85 % - 115 %). Acceptance criteria were fulfilled
	up to 1 day	102.7 %	101.6 %	
	up to 4 days	105.3 %	99.2 %	
	freeze/thaw cycles:	37.5 ng/ml	0.250 ng/ml	
	1 st cycle	107.2 %	108.8 %	
	2 nd cycle	103.5 %	104.0 %	
	3 rd cycle	104.8 %	98.4 %	
stored at RT:	37.5 ng/ml	0.250 ng/ml		
6 hours	100.0 %	94.4 %		
Final extract	stored for	37.5 ng/ml	0.250 ng/ml	
	1 hours at RT and 51 hours in the AS	98.1 %	92.4 %	

Source: Table generated by (b) (4) Project-No.: 307B17-Val, Table 1
Abbreviations: AS, autosampler; CV, coefficient of variation; IS, internal standard; LLOQ, lower limit of quantitation; QC, quality control; RD, relative deviation; RT, room temperature; ULOQ, upper limit of quantitation

Bioanalytical Method for ¹⁴C Radioactivity

A method for determining ¹⁴C radioactivity in human plasma by liquid scintillation counting was developed and validated by (b) (4) -024033/ (b) (4) -RD-559). The method had a 3-run validation, and the method was considered validated if the within-run, between-run, and overall precision were ≤15% (20% at the LLQ), and if the bias was between -15% and 15% (between -20% and 20% at the LLQ). The within-run, between-run, and overall coefficients of variation were not higher than 19% at LLQ and not higher than 5% at other QC levels. The overall bias of the heparin plasma method for the 1.00, 0.500, and 0.250 mL assay was between 5.2% and 16.3%. For hemolytic heparin plasma, the accuracy and precision results met the criteria except for the hemolytic samples at the LLQ, which showed an overall CV% >20% for the 1.00 mL assay and a bias >20% for the 0.250 mL assay. It was noted that hemolysis does not normally occur during plasma sample preparation, but if it were to occur, a high CV% or high bias is only observed at the LLQ, indicating that hemolysis generally has a low impact on the study results. The study also showed that both heparin and EDTA could be used as an anticoagulant, as the results for experiments measuring the effect of EDTA plasma samples did not deviate by more than 15% from the mean activity in heparin plasma samples for all 5 activity levels. One deviation occurred: for plasma, the quench curve used for efficiency corrections was not a ¹⁴C low level quenched standard set, but an in-house prepared quench curve was made. It was noted that the use of the in-house prepared quench curve significantly improved the assay method. In an amendment (b) (4) -034523), a 2 mL assay was added. For

heparin plasma, the within-run, between-run, and overall CV were all not higher than 11.4% for all ^{14}C -radioactivity levels. The overall bias was between 9.0% and 11.7%. For hemolytic plasma, the within-run, between-run, and overall CV were all not higher than 17.1% for all ^{14}C -radioactivity levels, and the overall bias was between -7.6% and +7.8%.

The validation of a method for the determination of total ^{14}C -radioactivity in human whole blood samples was determined at (b) (4) (Method Number (b) (4)-RD-1360). The method used liquid scintillation counting using low level counting. The validation range was 50.0 to 20000 dpm/mL for total ^{14}C -radioactivity. The matrix was human whole blood. Anticoagulants used included K_2 -EDTA, K_3 -EDTA, lithium heparin, and sodium heparin. The accuracy ranged from -4.6% to 14.5%, the precision ranged from 1.3% to 12.0%, the dilution as 10-fold and analysis was up to 200000 dpm/mL, and matrix variability was within criteria.

The validation of a method for determination of ^{14}C -radioactivity in human urine by liquid scintillation counting was determined at (b) (4)-024033/(b) (4)-RD-562). The method was selective for quenching of endogenous urine compounds for the 1.00 mL assay. The selectivity for the 2.0 mL urine assay was not within its specifications because the bias of the assay was >20% (i.e., 26.1%); however, it is expected that the high bias was due to an add-up of measurement errors because each sample is corrected for its own blank and the 6 independent samples were spiked at LLQ level. Because possible differences in transformed spectral index external standard (tSIE) values are corrected by the quench curve, the Applicant concluded that these results should be accepted. The method was considered validated if the within-run, between-run, and overall precision were $\leq 15\%$ (20% at the LLQ), and if the bias was between -15% and 15% (between -20% and 20% at the LLQ). Within-run, between-run, and overall CV were $\leq 16.3\%$ for all ^{14}C -radioactivity levels. The overall bias of the urine method was between 0.3% and 16.6%. For the 2.00 mL urine assay, the within-run, between-run, and overall CV were $\leq 18.1\%$ for all ^{14}C -radioactivity levels. The overall bias was between 3.6% and 15.8%. One deviation that occurred was that for urine, an in-house quench curve was used and significantly improved the assay method for determining the low level ^{14}C -radioactivity in human urine. The validation of a method for determination of ^{14}C -radioactivity in human feces by combustion and subsequent liquid scintillation counting was determined by (b) (4) (b) (4)-034723/(b) (4)-RD-605). The method was considered to be valid if within-run, between-run and overall precision were $\leq 15\%$ (20% at the LLQ level) and if the bias was between -15% and 15% (between -20% and 20% at the LLQ). For feces homogenized in 2% Arabic gum, the validated range was 50.0 dpm.g⁻¹ – 1000000 dpm.g⁻¹. Within-run, between-run, and overall CV were not higher than 14.7% for all ^{14}C -radioactivity levels in the validated range. Overall bias was between -6.3% to 8.6%. For feces homogenized in water, the validated range was 40.0 dpm.g⁻¹ – 1000000 dpm.g⁻¹. Within-run, between-run, and overall CV were not higher than 19.3% for all ^{14}C -radioactivity levels. Overall bias was between -12.6% to 4.0%.

An addendum was completed for the determination of ^{14}C -radioactivity in human urine and feces by (b) (4)-RD-562 / (b) (4)-RD-605 / (b) (4)-044173, S310.1.005) for the partial validation of a method for determination of ^{14}C -radioactivity in stabilized urine and feces samples. For precision, within-run, between-run, and total CV were calculated at each level, and the total CV could not exceed 15% (20% at the lower limit of quantification [LLOQ]). For accuracy, the overall bias was calculated at each level, and bias could not exceed $\pm 15\%$ (20% at LLOQ). The methods for determination of ^{14}C -radioactivity in

human urine in the presence of citric acid and human feces in the presence of 2 M sodium acetate were validated successfully.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

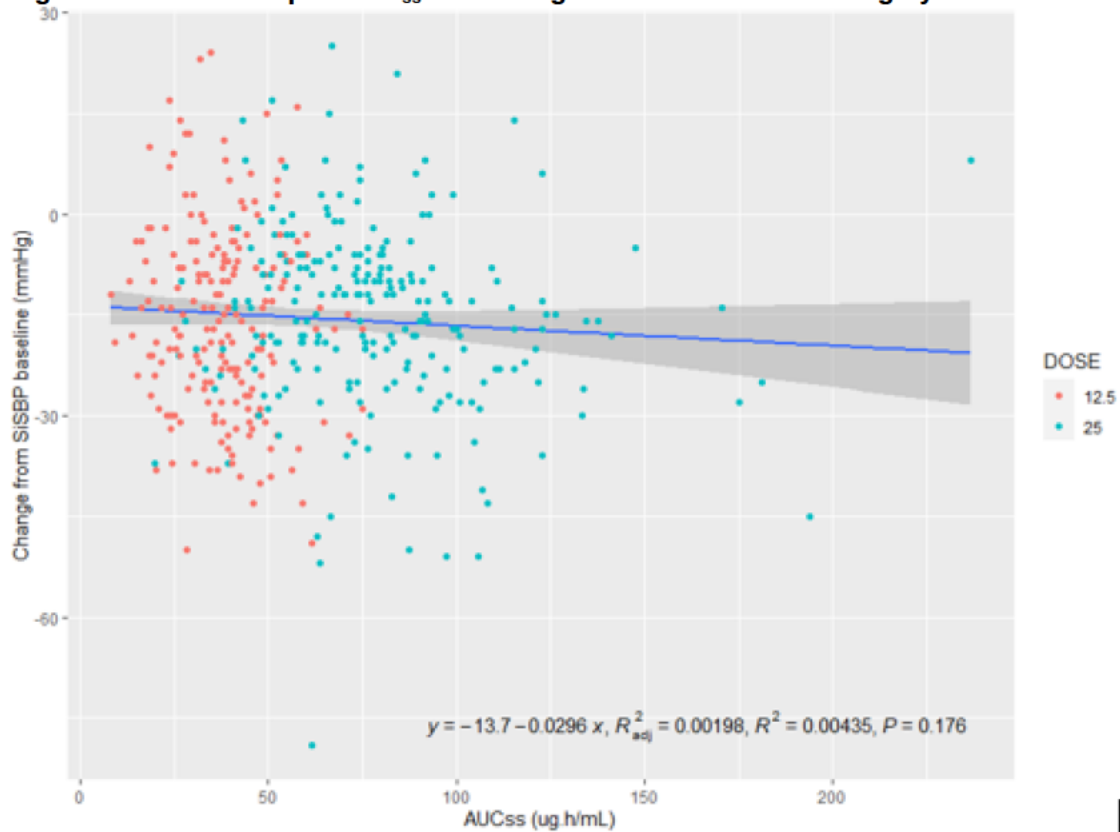
14.5.1. Executive Summary

The Applicant is seeking approval of aprocitentan, a dual ERA, for the treatment of hypertension in subjects who are not adequately controlled on other drugs. A population pharmacokinetic (PopPK) model was developed using data from 902 subjects receiving active treatment, including data from 251 subjects in Phase 1 studies, 226 subjects with essential hypertension in Phase 2, and 425 subjects with resistant hypertension in the Applicant's Phase 3 studies. The key pharmacometrics findings are summarized below.

- There does not appear to be a difference in efficacy between the 12.5 mg and 25 mg dose, as demonstrated by the flat exposure-response (E-R) relationship for the change from baseline in SiSBP¹¹ (see [Figure 22](#)). (b) (4)

¹¹ SiSBP was measured by unattended automatic office blood pressure measurement (uAOBPM), page 36 ([link](#))

Figure 22. Relationship of AUC_{ss} and Change From Baseline in Sitting Systolic Blood Pressure

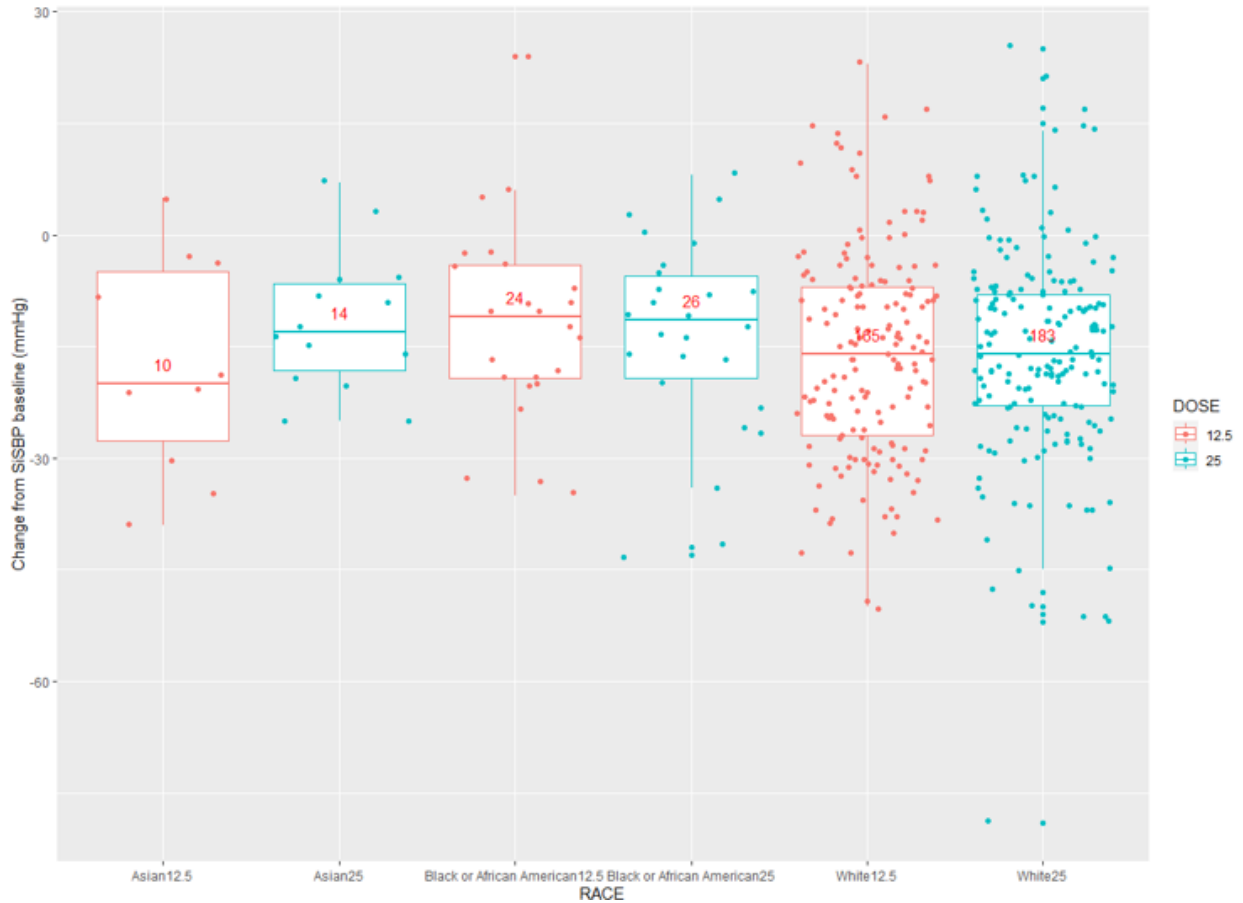


Source: Reviewer-independent assessment

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state, SiSBP, sitting systolic blood pressure

- There is no obvious difference in the median response between the 12.5 mg and 25 mg dose in subjects who are Black or African American, as shown in [Figure 23](#). (b) (4)

Figure 23. Relationship Between Race and Change From Baseline in Sitting Systolic Blood Pressure



Source: Reviewer-independent assessment
 Abbreviation: SiSBP, sitting systolic blood pressure

- The PopPK analysis suggests that no dosage adjustment is needed in patients with renal impairment (eGFR >15 mL/min/1.73 m²) or moderate hepatic impairment as shown in [Table 123](#) and [Table 124](#), respectively.

Table 123. Normalized AUC_{ss} Assessment for eGFR Groups

eGFR	Number of Subjects	AUC _{ss} (Geometric Mean)	Geometric CV%	Ratio%
15-30	16	3.8	38.7	135
30-45	26	3.6	21.3	126
45-60	54	3.3	37.1	115
60-90	411	2.9	33.9	104
90-maximum	452	2.7	35.9	95
90	21	2.8	34.4	100

Source: Reviewer-independent assessment
 Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; CV, coefficient of variation; eGFR, estimated glomerular filtration rate

Table 124. Normalized AUC_{ss} Assessment for HI Groups

HI Status	Number of Subjects	AUC _{ss} (Geometric Mean)	Geometric CV%	Ratio%
Healthy	972	2.8	35.7	100
Moderate HI	8	3.7	22	130

Source: Reviewer-independent assessment

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; CV, coefficient of variation; HI, hepatic impairment

14.5.2. Population PK Analysis

14.5.2.1. Review Summary

The Applicant's PopPK analysis for aprocitentan is acceptable to support the current submission. The Applicant's final PopPK model adequately described the aprocitentan concentrations, in which PopPK parameter estimates were estimated with acceptable precision as indicated by the relative standard errors (RSE) for total body clearance of drug (CL, 1.9% RSE), volume of distribution in central compartment (V_c, 0.4% RSE), volume of distribution in peripheral compartment (V_p, 2.4% RSE), intercompartment clearance (Q, 16.6% RSE) and Ka (7.3% RSE). The goodness-of-fit plots showed good agreement between the observed and the individual predicted concentrations without any obvious bias over time. The prediction-corrected visual predictive check plots showed good agreement between the observed and the simulated concentrations. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. For further comments on the utility of the model to support labeling and derive exposure metrics for exposure-response analyses, see [Table 125](#).

Table 125. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer's Comments
Utility to support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Based on a PopPK analysis, renal impairment, and moderate hepatic impairment do not have a clinically meaningful effect on the PK. Dose adjustment based on renal impairment and hepatic impairment is not required. Body weight was identified as a statistically significant covariate for CL, V _c , V _p , Q. Food effect was identified as a statistically significant covariate for absorption lag time and Ka.	The Applicant's draft labeling indicates that no dose adjustment is needed in patients with renal impairment (eGFR >15 mL/min/1.73 m ²) or in patients with moderate hepatic impairment. The Applicant's proposal is supported by the PopPK analysis and is acceptable.
	Extrinsic factor	NA	NA
Utility for deriving exposure metrics for exposure-response analyses	C _{min}		The Applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses (Table 129).

Source: Reviewer-independent assessment

Abbreviations: CL, clearance; C_{min}, minimum concentration; eGFR, estimated glomerular filtration rate, Ka, absorption rate constant; NA, not applicable; PK, pharmacokinetics; PopPK, population pharmacokinetics; Q, intercompartmental drug transfer; V_c, volume of distribution of central compartment; V_p, volume of distribution of peripheral compartment

14.5.2.2. Introduction

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

- Develop a population PK model describing aprocitentan plasma concentration over time at the population level and at the individual level.
- Investigate the relationship between covariates and model parameters.
- Quantify and visualize the influence of identified covariates on the concentration-time profile of aprocitentan via model-based simulations, enabling judgment about the clinical relevance of the covariates.

14.5.2.3. PopPK Model Development

Data

A total of 902 subjects receiving active treatment were included in the PK modeling data set, of which 251 subjects were enrolled in Phase 1 studies, 226 were enrolled in a Phase 2 study conducted in subjects with essential hypertension, and 425 were enrolled in a Phase 3 study conducted in subjects with resistant hypertension. For an overview of the studies, see [Table 126](#).

A total of 356 out of 8450 (4.2%) aprocitentan concentration measurements in the modeling dataset were below the limit of quantification; most of these measurements were predose measurements obtained in Phase 1 studies.¹² Measurements below the limit of quantification were treated by M4 method, which was set to the LLOQ of 5 ng/mL and treated as censored in the PopPK analysis. Predose PK measurements obtained prior to first study treatment administration were set to a value of 0.05 ng/mL (censored) and specified as a missing dependent variable in the modeling data set (i.e., not used for modeling).

In addition to the 8450 (94.4%) records, a total of 498 records (5.6%) were kept in the data set but flagged for exclusion for various reasons, such as extreme low values, missed dosing time, missed sampling time, etc.¹³

Agency Assessment

The Applicant excluded observations with extremely low values, which may affect parameter estimates of PopPK models. Model parameter estimates based on the inclusion of extremely low values and creatinine imputation were similar to those of the Applicant's final PopPK model. Therefore, the Applicant's final PopPK model is considered acceptable.

¹² IR ([link](#))

¹³ Applicant's poppk report ([link](#)), Page 20.

Table 126. Overview of Clinical Studies Contributing Data to PopPK Dataset

Study identifier and description	Study design	Treatments (Formulation)	Subjects	Planned PK sampling	Food status
AC-080-101 Single-center, three-part Phase 1 study to investigate the safety, tolerability, PK and PD of aproцитentan in healthy male and female subjects. (completed [D-15.519])	Part A (PILOT): • Single-center; • Open-label. Part B (SAD): • Single-center; • Double-blind; • Randomized; • Placebo-controlled; • Parallel-group; • Single-dose. Part C (MAD): • Single-center; • Double-blind; • Randomized; • Placebo-controlled; • Parallel-group; • Multiple-dose.	Part A: • Single dose of 5 mg aproцитentan. Part B: • Single dose of 25, 100, 300, 600 mg aproцитentan or placebo; • In the 100 mg dose group subjects returned to receive a single dose of 100 mg aproцитentan with food. Part C: • Multiple doses of 5, 25, 100 mg aproцитentan or placebo o.d. for 10 days. (Capsule)	Part A: • Planned and actual: 6 healthy male and female subjects. Part B: • Planned and actual: 8 healthy male and female subjects per dose level (6 on active / 2 on placebo per dose level). Part C: • Planned: – 8 healthy male and female subjects per dose level (6 on active / 2 on placebo per dose level); – Additionally, 8 healthy elderly male and female subjects receiving 100 mg aproцитentan o.d. • Actual: – 9 healthy male and female subjects in the 5 and 100 mg dose group; – 8 healthy male and female subjects in the 25 mg dose group; – 8 healthy elderly male and female subjects in the 100 mg elderly dose group.	Part A: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 36, 48, 72, 96, 120, 168, 216 h post study treatment administration. Part B: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 36, 48, 72, 96, 120, 168, 216 h post study treatment administration. Part C: Day 1: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15 h post-study treatment administration, Day 2: 0 (trough), 12, Day 3–5: 0 (trough), Day 8: 0 (trough), Day 10: 0 (trough), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 36, 48, 72, 96, 120, 168, 216 h post study treatment administration.	Part A: Fasted Part B: Fasted, except period 2 in the 100 mg dose group Part C: Fasted
AC-080-102 Multiple-dose study to evaluate potential body weight increase induced by fluid retention in healthy male subjects on a high-sodium diet. (completed [D-18.046])	• Single-center; • Double-blind; • Randomized; • Placebo-controlled; • Two-way cross-over; • Multiple-dose.	Subjects were randomized to 1 of 2 treatment sequences: A/B or B/A. A: either 10, 25, or 50 mg aproцитentan o.d. from Day 1 to Day 9. B: matching placebo o.d. from Day 1 to Day 9. In each treatment, subjects were on a high-sodium diet from Day –3 to Day 9. (Capsule)	Planned: Healthy male subjects on HSD. • 8 subjects at 10 mg vs placebo; • 8 subjects at 25 mg vs placebo; • 8 subjects at 50 mg vs placebo. Actual: • 9 subjects at 10 mg vs placebo; • 11 subjects at 25 mg vs placebo; • 8 subjects at 50 mg vs placebo. 23 subjects were available for the per-protocol set.	Day 1: 0 (pre-dose), 1, 2, 4, 6, 8, 10 h post-study treatment administration, Day 2, 3, 5, 8: 0 (trough), Day 9: 0 (trough), 1, 2, 4, 6, 8, 10 h post-study treatment administration, Day 20±1: 0 h (trough) post study start.	Fasted
AC-080-103 DDI study to investigate the effect of multiple-dose aproцитentan on the PK of the CYP3A4 substrate midazolam. (completed [D-17.248])	• Single-center; • Open-label; • Two-treatment; • Single-sequence; • Multiple-dose.	All subjects underwent the sequence A/B1/B2. A: single oral dose of 8 mg midazolam on Day 1. B1: single loading dose of 150 mg aproцитentan on Day 2 followed by o.d. 50 mg aproцитentan on Day 3–5. B2: single oral dose of 8 mg midazolam and 50 mg aproцитentan on Day 6. (Capsule)	Planned: 20 healthy male subjects to achieve at least 16 evaluable subjects. Actual: 19 evaluable healthy male subjects.	Day 3: 0 (pre-dose), Day 4–5: 0 h (trough) post study start.	Fasted

NDA 217686
TRYVIO (aprocitentan)

Study identifier and description	Study design	Treatments (Formulation)	Subjects	Planned PK sampling	Food status
AC-080-104 ADME study with ¹⁴ C-radiolabeled aprocitentan to investigate the mass balance, PK, and metabolism. (completed [D-18.105])	• Single-center; • Open-label; • Single-dose.	Single oral dose of 3.7 MBq (100 microcurie [¹⁴ C]) ¹⁴ C-radiolabeled aprocitentan administered as 1 capsule of 25 mg aprocitentan. (Capsule)	Planned and actual: 6 healthy male subjects.	0 (pre-dose), 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336 h post study treatment administration.	Fasted
AC-080-105 Phase 1 study to investigate the effect of severe RI on the PK of aprocitentan. (completed [D-18.125])	• Single-center; • Open-label; • Single-dose.	Single oral dose of 50 mg aprocitentan. (Capsule)	Planned and actual: Male and female subjects: • Group A: 8 healthy subjects; • Group B: 8 subjects with severe RI.	0 (pre-dose), 1, 2, 3, 4, 6, 7, 8, 10, 12, 16, 24, 48, 72, 120, 168, 216, 264, 312 h post study treatment administration.	Fasted
AC-080-106 DDI study to investigate the effect of aprocitentan at steady state on the PK of rosuvastatin in healthy male subjects. (completed [D-18.126])	• Single-center; • Open-label; • Two-treatment; • Single-sequence; • Multiple-dose.	All subjects underwent the sequence A/B1/B2. A: single oral dose of 10 mg rosuvastatin on Day 1. B1: from Day 5 to Day 12 subjects received 25 mg aprocitentan o.d. B2: Single oral dose of 10 mg rosuvastatin and 25 mg aprocitentan on Day 13. From Day 14 to Day 17 subjects received 25 mg aprocitentan o.d. (Capsule)	Planned and actual: 20 healthy male subjects. 17 subjects were available for the per-protocol set.	Day 5: 0 (pre-dose), Day 6–12: 0 (trough) h post study start.	Uncontrolled
ID-080-107 Multiple-dose study to investigate the tolerability, safety, and PK in healthy Japanese and Caucasian subjects. (completed [D-19.053])	• Single-center; • Double-blind; • Randomized; • Placebo-controlled; • Multiple-dose.	25 mg aprocitentan or placebo o.d. for 10 days. (Tablet A)	Planned and actual: • 10 healthy Japanese and 10 healthy Caucasian subjects. • In each ethnic group: – 5 males (4 on aprocitentan and 1 on placebo); – 5 females (4 on aprocitentan and 1 on placebo).	Day 1: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15 h post-study treatment administration, Day 2: 0 (trough), 12 h post-study treatment administration, Day 3–9: 0 (trough), Day 10: 0 (trough), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 48, 120, 216 h post-study treatment administration.	Fasted
ID-080-108 Study to assess the effect of multiple therapeutic and supratherapeutic doses of aprocitentan on the QT interval duration in healthy subjects (clinically completed [D-22.079])	• Single-center • Double-blind • Randomized • Placebo- and moxifloxacin-controlled • Multiple dose • 4-way crossover	All of the four treatments in random order: A: aprocitentan 25 mg o.d. for 10 days B: aprocitentan 100 mg o.d. for 10 days C: placebo o.d. for 10 days D: placebo o.d. for 9 days and a single dose of 400 mg moxifloxacin open-label on Day 10. (Tablet A)	Planned: 36 healthy male and female subjects to achieve at least 30 evaluable subjects. Actual: 48 healthy male and female subjects.	Day 1: –0.5, 1, 2, 3, 4, 6, 7, 8, 10, 12, 15 h post-study treatment administration, Day 2–9: 0 (trough), Day 10: –0.5 (trough), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24 h post study treatment administration.	Fasted

NDA 217686
TRYVIO (aprocitentan)

Study identifier and description	Study design	Treatments (Formulation)	Subjects	Planned PK sampling	Food status
ID-080-109 An open-label Phase 1 study to investigate the effect of moderate hepatic impairment due to liver cirrhosis on the pharmacokinetics of a single dose of 25 mg aprocitentan (completed [D-21.217])	- Two centers - Open-label - Single-dose	Single oral dose of 25 mg aprocitentan. (Tablet A)	Planned: Male and female subjects: 8 subjects with moderate hepatic impairment 8 healthy subjects Actual: 8 subjects with moderate hepatic impairment 9 healthy subjects	0 (pre-dose), 1, 2, 3, 4, 6, 7, 8, 10, 12, 15, 24, 72, 168, 216, 264, 312 h post study treatment administration.	Fasted
ID-080-110 A single-center, open-label, randomized, two-way crossover Phase 1 study to compare the single-dose pharmacokinetics of different tablet formulations of aprocitentan in healthy subjects (ongoing [D-21.333])	- Single-center - Open-label - Single-dose - Randomized - Two-way crossover	Single dose of 25 mg aprocitentan as two different formulations in random order. (Tablet A and Tablet B)	Planned: 36 subjects (at least 12 subjects of either sex) to achieve at least 30 evaluable subjects	0 (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 24, 72, 168, 216 h post study treatment administration per period.	Fasted
AC-080A201 Phase 2 dose-finding study with aprocitentan in subjects with essential hypertension. (completed [D-17.023])	- Multi-center - Double-blind - Double-dummy - Randomized. - Placebo- and active-reference, parallel group.	Treatment o.d. for 8 weeks in each 6 arms: 4 dose levels of aprocitentan: 5, 10, 25, and 50 mg, - Placebo; - Lisinopril 20 mg. (Capstule)	Planned: 540 subjects with essential hypertension (grade 1 and 2). Actual: 490 subjects with essential hypertension (grade 1 and 2).	Trough at Week 2 (Day 14 ± 3), Week 4 (Day 28 ± 3), Week 8 (Day 55 ± 5)	Uncontrolled

Study identifier and description	Study design	Treatments (Formulation)	Subjects	Planned PK sampling	Food status
ID-080A301 (PRECISION) Phase 3 study with aprocitentan in subjects with resistant hypertension (RHT) (ongoing [Idorsia 2020])	- Multi-center - Blinded - Randomized - Parallel group	Three parts. - Placebo o.d., aprocitentan 12.5 mg o.d., aprocitentan 25 mg o.d. randomized in 1:1:1 ratio (4 weeks) 25 mg o.d. (32 weeks)* - Withdrawal period. Placebo o.d., aprocitentan 25 mg o.d. randomized in 1:1 ratio (12 weeks)† (Tablet A)	Planned: 600 subjects with RHT.	Trough at Week 4 (Day 28 ± 2).	Uncontrolled

Source: Applicant's PopPK report, Page 218

No PK data is collected in these study parts

Tablet A and B are film-coated tablets containing drug substance with different (b) (4).

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ¹⁴C, carbon 14 isotope radiolabel; DDI, drug-drug interaction; h, hour; HSD, high-sodium diet; MAD, multiple-ascending-dose; o.d., once daily; PD, pharmacodynamics; PK, pharmacokinetics; PopPK, population pharmacokinetics; RHT, resistant hypertension; RI, renal impairment; SAD, single-ascending-dose

Table 127. Summary of Baseline Demographic Covariates for Analysis

Variable	Min.	10 th percentile	1 st quartile	Median	Mean	3 rd quartile	90 th percentile	Max.
Age (years)	18	30	45	55	53	65	71	84
Body weight (kg)	43.6	66.7	75.5	87.0	90.5	101.8	120	195.8
Height (cm)	124	158	165	172	172	179	183	199
BMI (kg/m ²)	18.2	23.4	26.1	29.7	30.7	34.7	39.1	63.9
Lean body weight (kg)	29.9	42.1	48.7	59.5	58.6	67.5	75.0	99.2
Fat mass (kg)	8.1	17.3	22.0	29.3	31.8	39.0	49.1	107.2
Creatinine concentration at baseline (μmol/L)	35	61	71	80	86	95	115	318
CL _{Cr} (mL/min)	26	67.1	86	110	113	135	161	323
eGFR (mL/min/1.73 m ²) [#]	17	59	72	89	89	104	122	197

Variable	Group (size)
Sex	Female (330), Male (572)
Race/ethnicity	American Indian or Alaska Native (4), Asian (33), Black or African American (183), Hispanic or Latino (3), Other/Not reported (2), White (677)
Hepatic impairment	Healthy (894), moderate (8)
eGFR category	≥15 & < 30 (16), ≥30 & < 45 (26), ≥45 & < 60 (54), ≥60 & < 90 (370), ≥90 (436)
Food status*	Fasted (264), fed (5), uncontrolled (671)
Formulation*	Capsule (373), Tablet A [#] (534), Tablet B [#] (33)
Disease status	Healthy (251), hypertension (651) of which essential hypertension (226) and resistant hypertension (425)
Study phase	Phase 1 (251), Phase 2 (226), Phase 3 (425)
Diabetes	Yes (258), No (644)

Source: Applicant's PopPK report, Page 19

eGFR calculated using the MDRD formula ([Levey et al. 1999](#)).

* The total number of subjects of 940 is larger than 902, as one subject can be both, fed and fasted, or receive different formulations in different periods of the same study.

Tablet A and B are film-coated tablets containing drug substance with different (b) (4).

Abbreviations: BMI, body mass index; CL_{Cr}, creatinine clearance; eGFR, estimated glomerular filtration rate; max., maximum; MDRD, Modification of Diet in Renal Disease; min., minimum

Base Model

The base model is a two-compartment PK model with absorption lag time (tlag), first-order absorption and first-order elimination from the central compartment.

Interindividual variability was modelled assuming a log-normal distribution for subject level random effects. The interindividual variability was considered for total body clearance of drug (CL), volume of distribution for central compartment (Vc), tlag, absorption rate constant (ka), volume of distribution of peripheral compartment (Vp) and intercompartmental drug transfer (Q).

Intra-individual variability was tested as combined additive and proportional error model on the dependent variable.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value, successful model convergence, and diagnostic prediction-corrected visual predictive check.

Covariate Analysis

Covariate parameters such as body weight, sex, age, formulation, race, etc. shown in [Table 128](#), were investigated.

Agency Assessment

Per FDA General Clinical *Pharmacology Considerations for Pediatric Studies for Drugs and Biological Product* ([Wang et al. 2012](#); [September 2022](#)), there are enough samples for subjects in renal groups and hepatic groups to target a 95% CI [confidence interval] of the geometric mean estimates of clearance and volume of distribution in each subgroup with at least 80% power.

Table 128. Covariate Analysis: Covariates That Were Assessed

Model parameter	Candidate covariates
Absorption parameters	<i>Food status (fed, fasted, uncontrolled)[#], formulation (capsule, tablet A, tablet B)[#]</i>
Volume(s) of distribution	<i>Age, sex[#], race[#], disease (healthy vs patient; healthy vs essential hypertension vs resistant hypertension)[#]</i>
Intercompartmental drug transfer	-
Drug clearance	<i>Age, sex[#], renal impairment (eGFR < 30, 30–60, > 60 mL/min/1.73 m²)[#], creatinine concentration, creatinine clearance, eGFR, hepatic impairment[#], race[#], disease (healthy vs patient; healthy vs essential hypertension vs resistant hypertension)[#], diabetes (healthy vs patient)[#]</i>

Source: Applicant's PopPK report, Page 15

Tablet A and B are film-coated tablets containing drug substance with different (b) (4)).

eGFR calculated with the MDRD formula ([Levey et al. 1999](#)).

[#] Categorical covariates are shown in italics. All other candidate covariates are continuous.

Abbreviations: eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PopPK, population pharmacokinetics; vs, versus

Software and Estimation Methods

Population PK modeling was performed using nonlinear mixed effects modeling techniques implemented in Monolix version 2021R1 ([Lixoft 2021a](#)). The stochastic approximation expectation-maximization (SAEM) algorithm was used for parameter estimation ([Delyon et al. 1999](#)). Exploratory graphics were created in R version 4.04. Simulations were performed with Simulx version 2021R1 ([Lixoft 2021b](#)) and Berkeley Madonna ([Marcoline et al. 2022](#)).

14.5.2.4. Final Model

The parameter estimates for the final PopPK model are listed in [Table 129](#). The goodness-of-fit plots for the final model are shown in [Figure 24](#). The prediction-corrected visual predictive check plot for the final covariate model with all data is shown in [Figure 25](#) (Stratified by dose), and estimate of interindividual variability and conditional weighted residual histograms for the final PopPK model are shown in [Figure 26](#).

The final PopPK model was a 2-compartmental model as parameterized with Tlag, CL, V2, V3, Q. An exponential model was used for interindividual variability, and a combined additive and proportional error model was used for intra-individual variability.

- Relative bioavailability (F) was 21.7% and 43.6% lower after administration of 300 and 600 mg, respectively, compared to doses of up to 100 mg.
- Food status was included as a covariate for absorption parameters tlag and ka.
- Clearance and volume parameters were found to increase with body weight, and clearance increased with higher eGFR, decreased with moderate hepatic impairment (HI), and was slightly higher in male subjects compared to female subjects.
- Aprocitentan clearance for a reference female subject versus a male reference subject with body weight of 87 kg (median in the modeling data set), no HI, and eGFR of 90 mL/min/1.73 m² was 0.342 versus 0.354 L/h, respectively.

Table 129. Population Pharmacokinetic Parameter Estimates for Final Models

Parameter (unit)	Description	Population parameters		IIV	
		Estimate	%RSE	Estimate	%RSE
t_{lag} (h)	Absorption lag time	0.593	3.3	0.171	39.4
IOV on t_{lag} (-)	Inter-occasion variability	0.446	6.9	-	-
Food status on t_{lag} (-)	Covariate effect (fed)	1.00	21.9	-	-
	Covariate effect (uncontrolled)	0.166	136		
k_a (1/h)	Absorption rate constant	0.657	4.8	0.445	13.0
IOV on k_a (-)	Inter-occasion variability	0.530	7.3	-	-
Food status on k_a (-)	Covariate effect (fed)	-0.305	96	-	-
	Covariate effect (uncontrolled)	-0.114	164	-	-
F (-)	Relative bioavailability	1*	-	0.168	4.5
Dose 300 mg on F (-)	Covariate effect	-0.245*	-	-	-
Dose 600 mg on F (-)	Covariate effect	-0.572 *	-	-	-
V_c/F (L)	Apparent volume of distribution, central compartment	16.2	0.4	0.024	15.3
Body weight on V_c/F (-)	Covariate effect	1*	-	-	-
CL/F (L/h)	Apparent clearance	0.291	1.9	0.290	3.7
Body weight on CL/F (-)	Covariate effect	0.75*	-	-	-
eGFR on CL/F (-)	Covariate effect	0.222	15.3	-	-
Moderate HI on CL/F (-)	Covariate effect	-0.232	45.2	-	-
Sex on CL/F (-)	Covariate effect (male)	0.0343	68.6	-	-
Q/F (L/h)	Apparent intercompartmental drug transfer	0.512	16.6	1.77	8.8
Body weight on Q/F (-)	Covariate effect	0.75*	-	-	-
V_p/F (L)	Apparent volume of distribution, peripheral compartment	3.1	2.4	0.175	12.9
Body weight on V_p/F (-)	Covariate effect	1*	-	-	-
Residual error terms					
a_1	Constant error	0.1*	-		
b_1	Proportional error	0.146	0.9		

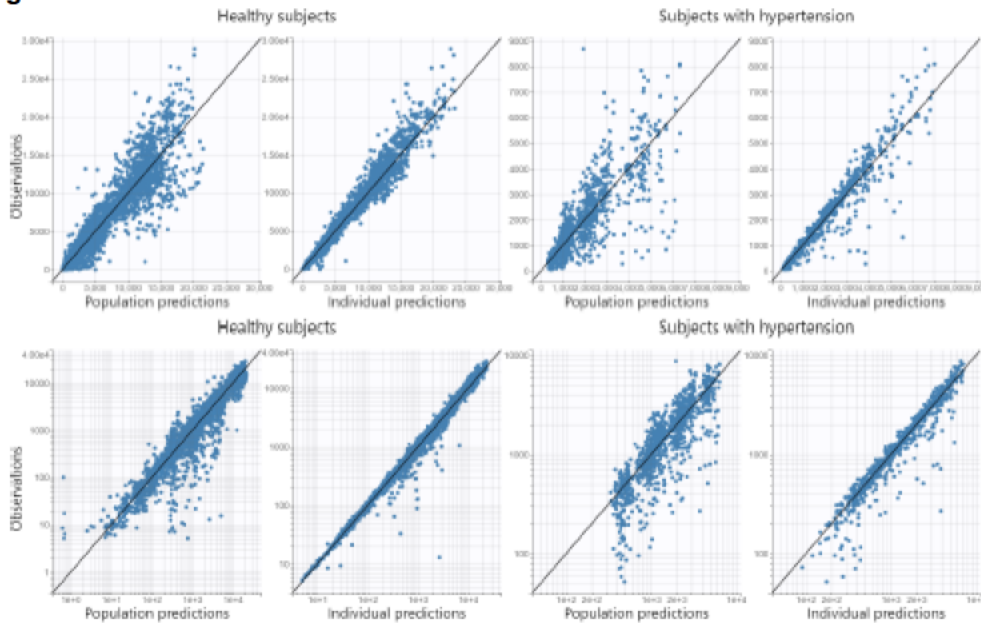
Source: Applicant's PopPK report, Page 30

*Parameter was fixed in the final model estimation.

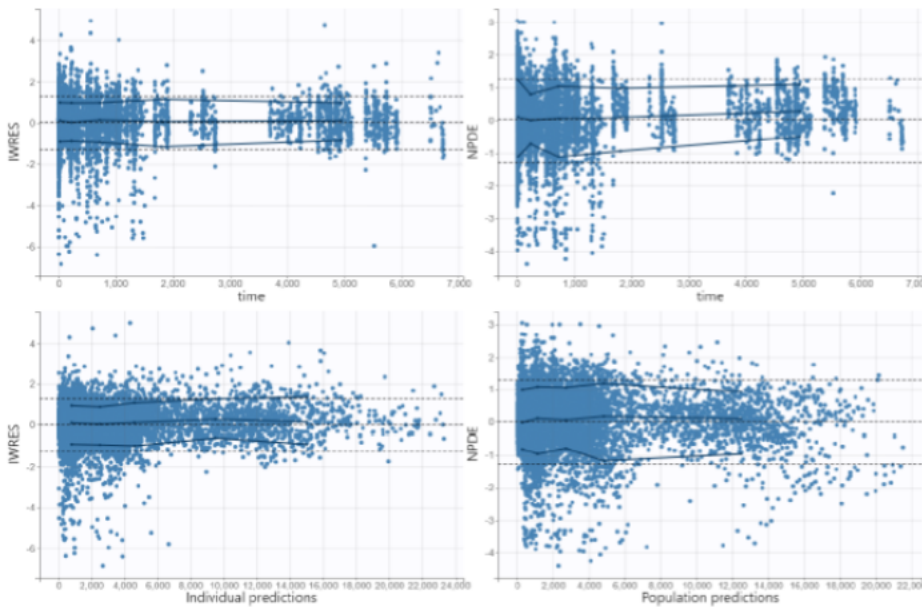
Covariates were normalized to 70 kg (standard allometric scaling), 90 mL/min/1.73m² (median in modeling data set), and a reference subject was fasted, had no HI, and was female.

Abbreviations: a_1 , constant error; b_1 , proportional error; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; F, relative bioavailability; HI, hepatic impairment; IIV, interindividual variability; IOV, inter-occasion variability; k_a , absorption rate constant; PK, pharmacokinetics; PopPK, population pharmacokinetics; Q/F, apparent drug transfer; RSE, relative standard error, t_{lag} , absorption lag time; V_c/F , apparent volume of distribution, central compartment; V_p/F , apparent volume of distribution, peripheral compartment

Figure 24. Goodness-of-Fit Plots for Final Covariate Model



Population predictions (left) and individual predictions (right) vs observations (all in ng/mL) on linear (top row) and logarithmic scales (bottom row) for subjects without (left two columns) and with (right two columns) hypertension. Black line: line of identity. Blue bullets depict data.



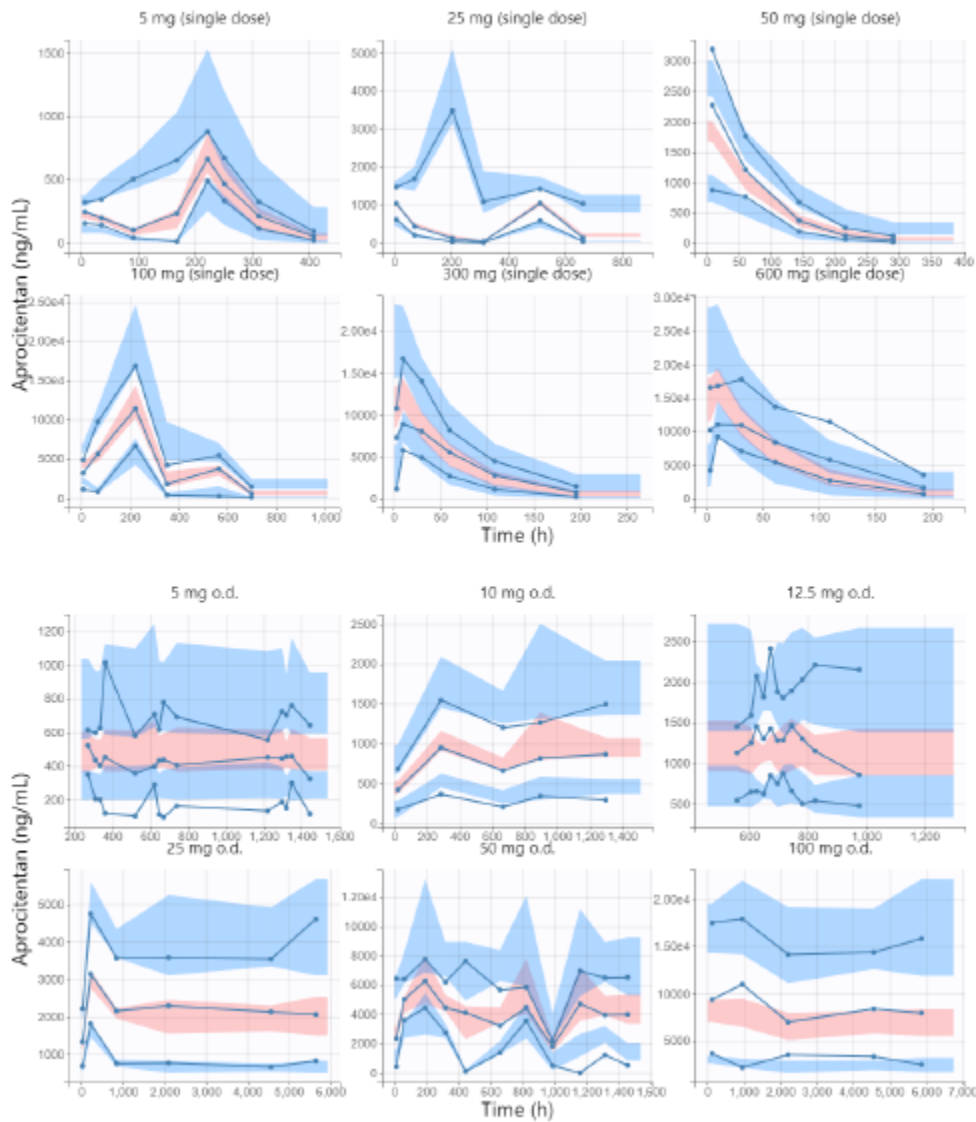
Bullets: residuals (left) and NPDE (right) vs time (top) and predicted concentration (bottom). Dark blue line: empirical median and 90% percentiles. Black dashed lines = NPDE and IWRES equals 0 and the predicted percentiles.

Source: Applicant's PopPK report Page 31, 33

Abbreviations: IWRES, individual weighted residuals; NPDE, normalized prediction distribution error, PK, pharmacokinetics; PopPK, population pharmacokinetics; vs, versus

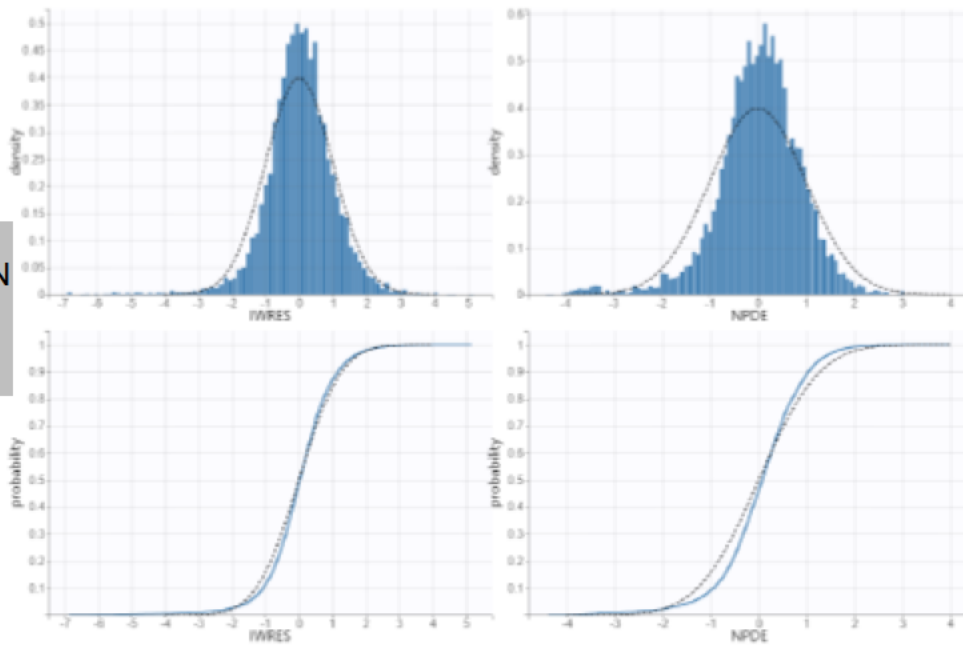
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Figure 25. Prediction-Corrected VPC Stratified by Dose



Source: Applicant's PopPK report, Page 32
Aprocitantan concentration (ng/mL) vs. time after first dose (h), stratified by dose (single dose vs. o.d. per study period).
Blue lines indicate empirical 10th, 50th, and 90th percentiles; shaded areas indicate 90% CIs of the predicted 10th (blue), 50th (red), and 90th (blue) percentiles, respectively.
Abbreviations: CI, confidence interval; o.d., once daily; PopPK, population pharmacokinetics; VPC, visual predictive check, vs., versus

Figure 26. ETA and CWRES Histograms for the Final PK Model



Top: empirical distribution (histogram) and estimated density function (dashed line). Bottom: empirical (solid blue line) and estimated (dashed line) cumulative density functions.

Source: Applicant's PopPK report, Page 33

Abbreviations: CWRES, conditional weighted residuals; ETA, estimate of interindividual variability; IWRES, individual weighted residuals; NPDE; normalized prediction distribution error; PK, pharmacokinetics; PopPK, population pharmacokinetics

Agency Assessment

The reviewer independently assessed covariates of the final model by Monolix (version 2021R1). HI and eGFR were not identified as significant covariates, which implies that dose adjustment for moderate hepatic impairment and renal impairment are not required. In contrast, formulation (capsule, tablet A, tablet B) was identified as a significant covariate as shown in [Table 130](#). The optimized model parameter estimates are shown in [Table 131](#). Model parameter estimates based on this model were, as a whole, similar to those obtained in the Applicant's final model. Therefore, the Applicant's final model is considered acceptable.

Table 130. Covariates Assessment

Model	OFV	Δ OFV
Final model	118626.32	0
Model without HI	118606.91	-19.41
Model without eGFR	118609.96	-16.36
Model without occasion	120553.68	1927.36
Model Without food on Ka	119310.08	683.76
Model with formulation on F	118239.15	-387.17
Model with formulation on F, ka	118203.12	-423.2
Model with formulation on F, tlag	118240.13	-386.19
Model with formulation on F, ka, tlag	118151.38	-474.94

Source: Reviewer's independent assessment

Abbreviations: Δ , change; eGFR, estimated glomerular filtration rate; F, relative bioavailability; HI, hepatic impairment; K_a , absorption rate; OFV, objective function value; t_{lag} , absorption lag time

Table 131. Optimized Final Population PK Model

Parameter (unit)	Description	Population parameters		IIV	
		Estimate	%RSE	Estimate	%RSE
t_{lag} (h)	Absorption lag time	0.69	5.0	0.2	28.9
IOV on t_{lag} (-)	Inter-occasion variability	0.42	6.5	-	-
Tablet A	Covariate effect	-0.29	23.6		
Tablet B	Covariate effect	-0.073	141		
Food status on t_{lag} (-)	Covariate effect (fed)	0.86	24.9	-	-
	Covariate effect (uncontrolled)	0.17	203		
k_a (1/h)	Absorption rate constant	0.54	6.7	0.43	12.5
IOV on k_a (-)	Inter-occasion variability	0.48	7.9	-	-
Tablet A	Covariate effect	0.35	25.6		
Tablet B	Covariate effect	0.21	61.7		
Food status on k_a (-)	Covariate effect (fed)	-0.32	81	-	-
	Covariate effect (uncontrolled)	0.34	52.7	-	-
F (-)	Relative bioavailability	1*	-	0.15	10.3
IOV on F	Inter-occasion variability	0.11	11.5	-	-
Tablet A	Covariate effect	0.16	9.3		
Tablet B	Covariate effect	0.083	37.2		
Dose 300 mg on F (-)	Covariate effect	-0.24*	-	-	-
Dose 600 mg on F (-)	Covariate effect	-0.572 *	-	-	-
V_c/F (L)	Apparent volume of distribution, central compartment	17.24	0.5	0.024	10.8
Body weight on V_c/F (-)	Covariate effect	1*	-	-	-
CL/F (L/h)	Apparent clearance	0.31	1.9	0.26	4.25
Body weight on CL/F (-)	Covariate effect	0.75*	-	-	-
eGFR on CL/F (-)	Covariate effect	0.16	20.1	-	-
Moderate HI on CL/F (-)	Covariate effect	-0.23	42.1	-	-
Sex on CL/F (-)	Covariate effect (male)	0.033	66	-	-
Q/F (L/h)	Apparent intercompartmental drug transfer	0.53	14.4	1.49	8.7
Body weight on Q/F (-)	Covariate effect	0.75*	-	-	-
V_p/F (L)	Apparent volume of distribution, peripheral compartment	3.32	3	0.27	9.8
Body weight on V_p/F (-)	Covariate effect	1*	-	-	-
Residual error terms					
a_1	Constant error	0.1*	-		
b_1	Proportional error	0.14	0.9		

Source: Reviewer's independent assessment

* Parameter was fixed in the final model estimation.

Covariates were normalized to 70 kg (standard allometric scaling), 90 mL/min/1.73m² (median in modeling data set), and a reference subject was fasted, had no HI, and was female.

Tablet A and B are film-coated tablets containing drug substance with different

(b) (4)

Abbreviations: a_1 , constant error; b_1 , proportional error; CL/F , apparent clearance; eGFR, estimated glomerular filtration rate; F, relative bioavailability; HI, hepatic impairment; IIV, interindividual variability; IOV, inter-occasion variability; k_a , absorption rate constant; PK, pharmacokinetics; PopPK, population pharmacokinetics; Q/F , apparent drug transfer; RSE, relative standard error, t_{lag} , absorption lag time; V_c/F , apparent volume of distribution, central compartment; V_p/F , apparent volume of distribution, peripheral compartment

14.5.2.5. Simulation

Simulations based on the final population PK model were employed to assess the clinical relevance of the covariates identified in the model development process. Aprocitentan concentration-time profiles were derived from model predictions for a reference female subject

of 87 kg, in the fasted state, without HI, and with an eGFR of 90 mL/min/1.73 m². The model-predicted concentration time-profiles without intersubject variability are shown in [Table 132](#).

Table 132. Covariate Effects on PK Parameters Following Administration of 25 mg Aprocitentan Once Daily for 10 Days

PK parameter	Covariate	Covariate value	Absolute exposure	Relative exposure
AUC _{τ, Day 10} (μg × h/mL)	Body weight (kg)	67	86.25	1.23
		87	70.39	1
		120	54.71	0.78
	eGFR (mL/min/1.73 m ²)	17	95.30	1.35
		30	86.43	1.23
		45	80.31	1.14
		60	76.10	1.08
		90	70.39	1
		120	66.50	0.94
	Food status	fasted	70.39	1
		fed	70.33	1.00
		uncontrolled	70.38	1.00
	Hepatic impairment	none	70.39	1
		moderate	85.56	1.22
	Sex	female	70.39	1
male		68.28	0.97	
C _{max, Day 10} (μg/mL)	Body weight (kg)	67	4.13	1.24
		87	3.34	1
		120	2.57	0.77
	eGFR (mL/min/1.73 m ²)	17	4.35	1.30
		30	3.99	1.19
		45	3.75	1.12
		60	3.57	1.07
		90	3.34	1
		120	3.18	0.95
	Food status	fasted	3.34	1
		fed	3.29	0.99
		uncontrolled	3.32	0.99
	Hepatic impairment	none	3.34	1
		moderate	3.96	1.19
	Sex	female	3.34	1
male		3.25	0.98	
C _{trough, Day 10} (μg/mL)	Body weight (kg)	67	3.00	1.21
		87	2.47	1
		120	1.94	0.79
	eGFR (mL/min/1.73 m ²)	17	3.47	1.40
		30	3.11	1.26
		45	2.87	1.16
		60	2.70	1.09
		90	2.47	1
		120	2.31	0.94
	Food status	fasted	2.47	1
		fed	2.53	1.00
		uncontrolled	2.48	1.02
	Hepatic impairment	none	2.47	1
		moderate	3.08	1.25
	Sex	female	2.47	1
male		2.38	0.96	

PK parameter	Covariate	Covariate value	Absolute exposure	Relative exposure
t _{max} , Day 10 (h)	Body weight (kg)	67	4.3	1.00
		87	4.3	1
		120	4.4	1.02
	eGFR (mL/min/1.73 m ²)	17	4.4	1.02
		30	4.4	1.02
		45	4.4	1.02
		60	4.3	1.00
		90	4.3	1
		120	4.3	1.00
	Food status	fasted	4.3	1
		fed	6.2	1.09
		uncontrolled	4.7	1.44
	Hepatic impairment	none	4.3	1
		moderate	4.3	1.00
	Sex	female	4.3	1
male		4.3	1.00	

Source: Applicant's PopPK report, page 36

AUC: Exposure over one dosing interval of 24 h on Day 10 (steady-state). Reference subject is a female subject of 87 kg body weight with eGFR of 90 ml/min/1.73 m² in fasted state without hepatic impairment.

Abbreviations: AUC_T, area under the concentration-time curve for a dosing interval T; C_{max}, maximum plasma concentration; C_{trough}, trough concentration (at time of next dose event); eGFR, estimated glomerular filtration rate; PK, pharmacokinetics, PopPK, population pharmacokinetics; t_{max}, time to reach maximum concentration

Agency Assessment

The Applicant's simulation did not consider intersubject variability, which is required to predict individual exposures. Therefore, the reviewer independently simulated individual exposures with intersubject variability, which is used to assess exposures of patients with renal impairment, patients with hepatic impairment, and formulations. AUC_{ss} was calculated based on F1, CL and dose, in which doses (300 mg and 600 mg) were excluded for their lower F1 values compared to doses ≤100 mg. In order to summarize the AUC_{ss} under different groups, the AUC_{ss} was normalized by AUC_{ss}/dose. The normalized AUC_{ss} ratios among eGFR, shown in [Table 133](#), are similar to those obtained via the Applicant's evaluation, in which eGFR (90 mL/min/1.73 m²) was treated as a reference. The normalized AUC_{ss} ratio between moderate hepatic impairment and healthy subjects, shown in [Table 134](#), is a little higher than that of the Applicant's simulation (130 versus 122). The normalized AUC_{ss} ratios among formulations (capsule, tablet A, tablet B) are shown in [Table 135](#). As shown in the table, normalized AUC_{ss} of the tablet A and tablet B have similar geometric means, while the normalized AUC_{ss} of the capsule has a lower geometric mean.

Table 133. Normalized AUC_{ss} Assessment for eGFR Groups

eGFR	Number of Subjects	AUC _{ss} (Geometric Mean)	Geometric CV%	Ratio%
[15- 30)	16	3.8	38.7	135
[30- 45)	26	3.6	21.3	126
[45- 60)	54	3.3	37.1	115
[60- 90)	411	2.9	33.9	104
(90-max)	452	2.7	35.9	95
90	21	2.8	34.4	100

Source: reviewer independent assessment

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; CV, coefficient of variation; eGFR, estimated glomerular filtration rate

Table 134. Normalized AUC_{ss} Assessment for HI Groups

HI Status	Number of Subjects	AUC _{ss} (Geometric Mean)	Geometric CV%	Ratio%
Healthy	972	2.8	35.7	100
Moderate HI	8	3.7	22	130

Source: reviewer independent assessment

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; CV, coefficient of variation; HI, hepatic impairment

Table 135. Normalized AUC_{ss} Assessment for Formulations

Formulation	Number of Subjects	AUC _{ss} (Geometric Mean)	Geometric CV%	Ratio%
Capsule	372	2.6	35.9	88.3
Tablet A	575	3	35.4	100
Tablet B	33	3.1	17.1	104

Source: reviewer independent assessment

Tablet A and B are film-coated tablets containing drug substance with different (b) (4)

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady-state; CV, coefficient of variation

Agency Assessment

Based on the model simulation, the highest difference among the normalized AUC_{ss} ratios assessment among groups (moderate hepatic impairment versus healthy, renal impairment versus healthy) is 35%, which is not clinically meaningful. Therefore, no dose adjustment is needed for patients with renal impairment (eGFR >15 mL/min/1.73 m²) and patients with moderate hepatic impairment.

14.5.3. Exposure-Response Relationship

The primary efficacy endpoint in the Phase 3 study (PRECISION)¹⁴ was the change from baseline at Week 4 of the double-blind treatment period in mean trough SiSBP. The reviewer conducted an E-R analysis between AUC_{ss} (estimated for the 12.5 mg and 25 mg dose based on the PopPK model) and the change from baseline in SiSBP at Week 4 in the Phase 3 study. As shown in [Figure 27](#), the E-R relationship appears to be flat over the 12.5 mg and 25 mg dose range and the p-value (0.176) of AUC_{ss} slope is not statistically significant. The relationship between race and response (change from baseline in SiSBP at week 4) was also assessed and is shown in [Figure 28](#). As indicated by the boxplots, there does not appear to be an obvious difference in median response between the 12.5 mg and 25 mg dose in subjects who are Black or African American.

¹⁴ id-080a301-body report ([link](#))

Figure 27. Relationship Between AUC_{ss} and Change From Baseline in Sitting Systolic Blood Pressure



Source: reviewer independent assessment

The AUC_{ss} values were predicted based on the PopPK model.

Abbreviations: AUC_{ss} , area under the concentration-time curve at steady-state; PopPK, population pharmacokinetics; SiSBP, sitting systolic blood pressure

Figure 28. Relationship Between Race and Change From Baseline in Sitting Systolic Blood Pressure for 12.5 mg and 25 mg Doses



Source: reviewer independent assessment
The number in the box plot is the number of subjects per group
Abbreviation: SiSBP, sitting systolic blood pressure

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Important Study Dates

The study enrolled its first subject on June 18, 2018, and the last subject had their last visit on April 25, 2022. The database lock for PRECISION study occurred on May 12, 2022.

15.2. Protocol Amendments

The clinical protocol was amended globally twice. An overview of these amendments is provided in the table below.

Table 136. Overview of Integrated Protocol Amendments, PRECISION Study

Amendment	Subjects Randomized n (%)	Summary of Significant Changes
Amendment 1 (protocol version 2), September 19, 2018.	286 (39%)	Exclusion of subjects with severe hepatic impairment added to exclusion criterion 16. Update to Section 4.5.2, acceptable methods of contraception, to comply with the Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials requiring a highly effective contraception method. Therefore, option 3 (combination of diaphragm with spermicide or cervical cap with spermicide with male condom) was removed from Section 4.5.2. Update to Section 5.2.3.2 (diuretics for fluid retention) to provide more guidance for diagnosis of fluid retention cases requiring treatment with diuretics. Added creatine kinase to the blood chemistry parameters for monitoring of potential myopathy/rhabdomyolysis. Exclusion criterion 5: Added atrial fibrillation to this criterion. This criterion was mistakenly missed in protocol Version 1. It ensures an accurate recording of ambulatory blood pressure monitoring. Exclusion criterion 16: Increased the NT-proBNP threshold from 200 pg/mL to 500 pg/mL. (It became clear, during the initial experience of Screening, that a large proportion of subjects with resistant hypertension (RHT) have values of NT-proBNP exceeding 200 pg/mL with no evidence of frailty, serious cardiac dysfunction, or heart failure. Exclusion criterion 18: The NT-proBNP exclusion criterion 18 at Randomization has been removed since it is not expected that the medical condition of subjects who fulfill all inclusion/exclusion criteria, and are successfully entered in the study, will deteriorate between Screening and Randomization.
Amendment 2 (protocol version 3), February 27, 2020.	420 (58)	Changed inclusion criteria 4 to not require a diuretic as one of the three antihypertensive classes for enrollment. This change was implemented to improve recruitment. Subjects were still placed on diuretic therapy as part of SBAT. Changed inclusion criteria 11 to allow for stable dose of SBAT for at least one week before the end of the RI period (previously stable for entire RI period)

Amendment	Subjects Randomized n (%)	Summary of Significant Changes
Global COVID-19 protocol amendment April 8, 2020	451 (62)	Expanded exclusion criteria 5 to include clinically significant unstable cardiac disease <u>at screening or in the past</u> and expanded definition of congestive heart failure to include NYHA stage II with relevant mitral valve insufficiency and/or aortic stenosis. Exclusion criteria 11 (Treatment with any medication which may affect BP) was expanded to also exclude treatment with high dose of loop diuretics (i.e., furosemide greater than 80 mg/day, or equivalent dosage of other loop diuretics). The second component of the study-specific discontinuation criterion for renal failure was modified from $\geq 30\%$ decreased eGFR to 2X increase in serum creatinine to avoid discontinuation of subjects due to potentially transient eGFR reduction. Removal of erythropoiesis-stimulating agents and psychiatric drugs from the list of the forbidden medications and adding them to allowed medications with the provision that they have been initiated and the dose has been stable at least 4 weeks prior to the screening visit, and that the dose is kept stable until the end of treatment. A global protocol addendum was issued to address the conduct of the study during the COVID-19 pandemic: measures and instructions, in line with health authority guidelines, were introduced to preserve subject safety, trial integrity and interpretability, and compliance with regulatory requirements.

Source: Clinical Study Protocols for PRECISION study

Abbreviations: BP, blood pressure; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; n, number of subjects; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RHT, resistant hypertension; RI, run-in; pleasetandard background antihypertensive therapy

15.3. Study Administrative Structure

Independent Data Monitoring Committee

The independent data monitoring committee (IDMC) was composed of 4 external experts with experience and expertise in the cardiovascular domain, statistical methodologies, safety monitoring, and overseeing randomized clinical studies. The IDMC was fully operational prior to enrollment of the first subject in the study. The IDMC had overall responsibility for safeguarding the interests of subjects by monitoring unblinded safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study was conducted to the highest scientific and ethical standards. Unblinded data were delivered to the IDMC by an Independent Statistical Analysis Center. The details of the IDMC organization, roles, and responsibilities, and conduct of meetings were defined in the IDMC charter.

Each meeting begins with an open session that Applicant representatives and coordinating investigators could attend. Data presented in the open session could include recruitment status, clinical study conduct (e.g., frequency of protocol deviations, withdrawal of consent from study, lost to follow-up, subject discontinuation, list of serious adverse events [AEs]), protocol amendments, communications with Health Authorities and any other metrics if needed. This was followed by a closed session, in which the IDMC discussed the unblinded results. A member of the Independent Statistical Analysis Center attended the closed session meeting (e.g., to present results and answer questions).

IDMC met nine times over the course of the study and conducted nine unblinded data reviews. Following evaluation of subject data during the third IDMC meeting (February 3, 2020), the IDMC recommended that subjects receiving treatment with high doses of loop diuretics be excluded from participation in the study. A letter was sent to the investigators on February 19, 2020 to exclude subjects with high doses of loop diuretics and exclusion criterion #11 was amended accordingly (*Global Protocol Amendment 2*).

See Section [15.5](#) for information on the administrative structure as relates to preparing the NDA submission and/or blinding related issues.

Independent Central Adjudication Committee

The CAC was composed of 3 external experts with experience in cardiovascular / renal medicine and expertise in the assessment of clinical events within a study. The CAC members were responsible for adjudicating, in a standardized and blinded fashion, all AEs/serious AEs identified by the Investigator or Sponsor which indicated potential major adverse cardiovascular events (MACE)-plus. MACE was defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. MACE-plus included, in addition, hospitalization for heart failure. The details of the CAC organization, roles and responsibilities, and adjudication process were described in the CAC charter.

15.4. Study Assessments

Baseline Values

All baseline blood pressure and laboratory measurements were collected during the run-in period (Day -1). Baseline is defined as the last available measurement before or on the day of randomization. DB-WD baseline (Week 36) is defined as the last available measurement before or on the day of rerandomization. If both date and time of the measurement are collected, baseline is the last measurement up to the date and time of randomization. If only the date is collected, baseline is the last measurement before the date of randomization.

uAOBPM

An automatic oscillometric sphygmomanometer was provided to each site by the vendor and had to be managed by qualified personnel. Wherever possible, the same person used the device for a given subject at each visit. Sitting BP, standing BP, and pulse rate were measured noninvasively throughout the study using this device, as described below.

BP was required to be measured at trough (i.e., before taking study treatment and standard background antihypertensive therapy [SBAT]), at around the same clock time, at each visit. Measurements were to be recorded from the same arm of the subject each time, using the appropriate cuff size as determined during screening.

Details on the blood pressure procedure, including the device to be used, subject preparation (e.g., arm selection, arm position, cuff size) were detailed in the BP laboratory manual and followed the American Heart Association guidelines/Canadian Education Program on Hypertension ([Pickering et al. 2005](#); [Daskalopoulou et al. 2012](#)). Automated office blood pressure measurement data was electronically transferred to the central BP laboratory and subsequently to the Applicant.

Sitting BP: The uAOBPM device recorded 5 BP readings (SiSBP and SiDBP), with preset time intervals between them. The first reading was taken after the subject had been sitting undisturbed in a quiet place for 5 minutes; this reading was excluded, and the device generated an average (mean trough) of the remaining four readings, taken at 1 minute intervals, for each variable.

Standing BP: monitoring of orthostatic hypotension was performed by measuring SBP and DBP twice, approximately 1 and 3 minutes after standing.

Pulse rate: measured at each visit at the same time as BP, while sitting. The last value recorded was used for analysis.

ABPM

ABPM devices were provided to each site by the central vendor. Subjects were required to attend the site on 2 consecutive days for each of the following visits:

- Baseline – End of the placebo run-in (RI) period; Visit 4 / Day –1
- End of DB Part 1 – Visit 6 / Week 4 (Day 28±2 d)
- End of single-blind (SB) Part 2 – Visit 11 / Week 36 (Day 252±12 d)
- During DB-WD Part 3 – Visit 13 / Week 40 (Day 280±4 d)

On the first day, after all visit assessments had been performed, the ABPM device was applied to the subject who then took the study treatment and SBAT in the presence of study personnel (i.e., direct observed treatment). The following day, the subject returned to the site to have the ABPM device removed. The ABPM device was automatically programmed to inflate every 20 minutes during the day (06:00–21:59) and every 30 minutes during the night (22:00–05:59), resulting in 64 readings over a 24 h period (48 during the day, 16 during the night). The main evaluation of ABPM data was performed based on recordings with at least 70% valid readings and a total duration of at least 21 h.

Home BP Measurement

HBPM devices were provided to each site and could be lent to subjects to monitor their own BP at home throughout the study, as per the Investigator's judgment. Subjects who were given an HBPM device were instructed on its use; and informed that they had to measure their BP in the event of any severe symptoms related to hypertension (headache, vomiting, or nosebleeds) or orthostatic hypotension (light-headedness, presyncope, or dizziness).

Subjects were required to record their data (SBP/DBP values, time and date of measurement, and time of study treatment intake) on the card provided with the HBPM device, for 3 days in a row. If symptoms were still present on the third day, subjects were instructed to contact the study site.

Data recorded by subjects at home were filed in hospital charts only, not in the electronic case report form (eCRF) and were not provided to the Applicant.

During the COVID-19 pandemic, if subjects were not allowed or not willing to travel to the investigator site, remote visits (i.e., phone/video calls or home visits) were conducted. Subjects were requested to measure their BP on the day before the scheduled remote visit, using either the HBPM device provided to them for the study or their own BP device. As described above, subjects were required to record their BP data on the HBPM card, or in a notebook (source document), and then to provide these values to the study site staff during the remote visit. The data were recorded in the subject's medical chart, verified against the source at the next on-site visit, and entered in the eCRF.

Schedule of Assessments

Screening

The screening period lasted up to 12 weeks, and the following assessments were obtained: demographics/medical history, physical examination, concomitant medications, height/weight, 12-lead electrocardiogram (ECG), hematology and chemistry laboratory assessments (see table below for details), pregnancy test, urinalysis (for urine albumin-to-creatinine ratio [UACR]), and uAOBPM.

Run-In

The run-in period lasted 4 weeks, and the following assessments were obtained: physical examination, concomitant medications, weight, 12-lead ECG, hematology and chemistry laboratory assessments (see table below for details), pregnancy test, urinalysis (for UACR), urinalysis (to monitor adherence), uAOBPM, and ABPM.

DB Treatment

The DB treatment period lasted for 4 weeks, and the following assessments were obtained: physical examination, concomitant medications, weight, 12-lead ECG, hematology and chemistry laboratory assessments including NT-proBNP (see table below for details), pregnancy test, urinalysis (for UACR), urinalysis (to monitor adherence), uAOBPM, and ABPM (Week 4).

SB Treatment

The SB treatment period lasted for 32 weeks, and the following assessments were obtained: physical examination, concomitant medications, weight, 12-lead ECG, hematology and chemistry laboratory assessments including NT-proBNP (see table below for details), pregnancy test, urinalysis (for UACR), urinalysis (to monitor adherence), uAOBPM, and ABPM (Week 36). During the SB aprocitentan part, urine pregnancy tests were performed monthly (i.e., between scheduled visits) at home with kits provided to the subject.

DB-WD Treatment

The DB-WD treatment period lasted for 12 weeks, and the following assessments were obtained: physical examination, concomitant medications, weight, 12-lead ECG, hematology and chemistry laboratory assessments including NT-proBNP (see table below for details), pregnancy test, urinalysis (for UACR), urinalysis (to monitor adherence), uAOBPM, and ABPM (Week 40).

Follow-Up

Following completion of the treatment period, subjects entered the 30-day follow-up period where study medication will be discontinued, except for SBAT. The following assessments were obtained during the follow-up period: physical examination, concomitant medications, weight, 12-lead ECG, hematology and chemistry laboratory assessments including NT-proBNP (see table below for details), pregnancy test, urinalysis (for UACR), and uAOBPM.

Table 137. Laboratory Parameters, PRECISION Study

Parameter	Components	Notes
Hematology	Hemoglobin, hematocrit, erythrocyte count, reticulocyte count, leukocyte count with differential counts, platelet counts, and mean corpuscular volume	
Chemistry	ALT, AST, ALP, bilirubin and direct bilirubin, cholesterol, triglycerides, HDL, LDL, creatinine, creatine kinase, eGFR, urate, albumin, protein, glucose, sodium, potassium, and NT-proBNP.	Creatine kinase was added in Global Protocol Amendment 1. NT-proBNP was added in Global Protocol Amendment 1.
Pregnancy	Serum pregnancy tests for women of childbearing potential were performed at all on-site visits during the study (except Weeks -2, 2 and 38) and analyzed by the central laboratory.	During the SB aprocitentan part, urine pregnancy tests were performed monthly (i.e., between scheduled visits) at home with kits provided to the subject.
Cardiac markers	NT-proBNP, MR-proANP, and troponin I were evaluated to explore whether aprocitentan had any effect on heart overload, and on micro- and macrovascular complications,	Only obtained at the end of placebo RI period (Day -1), at the end of DB Part 1 (Week 4), during SB Part 2 (Week 20 and Week 36), and during DB-WD Part 3 (Week 40). In addition, NT-proBNP was also measured at Screening (Visit 1), Visit 7 (Week 6), Visit 8 (Week 12), Visit 10 (Week 28), Visit 14 (Week 44), Visit 15/EOT (Week 48), and Visit 16/EOS (EOT plus 30 days) as part of central laboratory assessments.

Source: PRECISION Study Clinical Protocol version 3 dated February 27, 2020

A central laboratory was used for all protocol-mandated hematology, clinical chemistry, and urinalysis tests, including retests due to laboratory abnormalities and tests performed at unscheduled visits. Two samples were drawn at the end of the placebo RI period (Day -1): One for the central laboratory, and one for a local laboratory. Eligibility for randomization was determined based on local laboratory results (hemoglobin, creatinine for eGFR, AST/ALT, and pregnancy test), which were recorded in the eCRF. Abbreviations: ALT, alanine transaminase; ALP, alkaline phosphatase; AST; aspartate transferase; DB, double-blind; DB-WD, double-blind withdrawal; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MR-proANP; midregional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; RI, run-in; SB, single-blind

15.5. Study Procedures

Randomization

Randomization was performed through an interactive response technology (IRT). For each part of the study, the investigator/delegate contacted the IRT system for allocation of subject numbers, treatment bottle numbers, and subject randomization/erandomization numbers, as described below.

The IRT system was handled by an independent vendor which generated two randomization lists, one for DB Part 1 and one for DB-WD Part 3. At Visit 1 (Screening), after a subject had signed their ICF, the IRT system allocated a 7-digit subject number, which differed from the 5-digit randomization number. For subjects who were rescreened, a new subject number was assigned.

Screening

During the screening period, a subject's individual background antihypertensive medication (except beta-blockers, if present) was standardized by switching to SBAT, which was assigned via the IRT system. At the first run-in visit, the IRT system assigned the treatment bottle number for the 4-week placebo RI period.

DB Treatment

At Visit 4 / Randomization (Day 1), the IRT system randomized the subject to aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo, in a 1:1:1 ratio. The IRT assigned a randomization number to the subject and a bottle number which matched the treatment arm as assigned on the randomization list.

SB Treatment

At the end of DB Part 1 (Week 4), the IRT system assigned the first treatment bottle numbers for the 32-week SB Part 2 (25 mg). At each subsequent visit when single-blind treatment was dispensed, the IRT assigned the treatment bottle numbers.

DB-WD Treatment

At the end of SB Part 2 (Week 36), the IRT system rerandomized the subject to aprocitentan 25 mg or placebo in a 1:1 ratio. Rerandomization was stratified according to randomized treatment in DB Part 1 (which was not revealed). The IRT system assigned a scrambled, rerandomization number to the subject and bottle numbers which matched the treatment arm as assigned on the rerandomization list. At each subsequent visit when DB-WD treatment was dispensed, the IRT assigned the treatment bottle numbers according to the assigned treatment arm.

Blinding and Unblinding

Blinding

Two parts of the study were performed in a single-blind fashion: the placebo RI period prior to randomization, and SB Part 2. Study personnel were not permitted to inform subjects of the treatment received. Two parts were performed in a double-blind fashion: DB Part 1 and DB-WD Part 3. The Investigator and study personnel, subjects, CRAs, Sponsor personnel, and vendor/clinical research organization (CRO) personnel involved in the conduct of the study remained blinded to the treatment until database lock. Until the time of unblinding for final data analysis, the randomization/rerandomization lists were kept strictly confidential and were accessible only to Sponsor-authorized and CRO personnel who were not involved in the conduct of the study: IRT vendor personnel (responsible for clinical study supply distribution; subject level); the Sponsor's Pharmaceutical Development department personnel (clinical study supply distribution; depot level); the Sponsor's bioanalytical and biomarker laboratories; and the Independent Statistical Analysis Center and IDMC.

The Sponsor notes that the study treatment was provided as tablets and that the investigational treatment and its matching placebo were indistinguishable, and all treatment bottles were packaged in the same way.

Unblinding

Final analyses: Randomization information was made available for data analysis only after database closure.

IDMC review: The Independent Statistical Analysis Center delivered unblinded data summaries to the IDMC for their review.

Serious, unexpected, and suspected adverse reaction (SUSAR): When a SUSAR occurred for a subject participating in the study, the Sponsor's Global Drug Safety department requested the unblinding of the treatment assignment. The treatment assignment was not communicated to site personnel, subjects, other Sponsor personnel, or any vendor/CRO personnel involved in the conduct of the study. Unblinded SUSAR information was provided to respective health authorities, in addition to Independent Ethics Committees/Institutional Review Boards (as per each committee's/board's specific requirements). SUSARs were reported to investigators in a blinded fashion.

Emergency: Emergency unblinding did not occur during this study.

Dosing

For Part 1 of the study, dosages of 12.5 and 25 mg once daily were administered. For Parts 2 and 3, the aprocitentan dose administered was 25 mg once daily. Study treatment dose adjustments were not permitted. Study treatment could be temporarily interrupted in response to an AE, or other reasons (e.g., diagnostic or therapeutic procedure, a laboratory abnormality, study treatment forgotten). Interruptions of study treatment were no longer than 7 consecutive days during DB part and DB-WD part.

The decision to prematurely discontinue study treatment could be made by the subject, the Investigator, or Sponsor personnel. The main reason (e.g., AE, hypertension grade 3) was documented in the eCRF. Study-specific criteria for interruption / premature discontinuation of study treatment included hypertension (mean SiSBP ≥ 180 mmHg and/or mean SiDBP ≥ 110 mmHg measured by automated office blood pressure measurement and confirmed by repeat measurement), renal failure (confirmed eGFR < 15 mL/min/1.73m² or confirmed decrease of $\geq 30\%$ from baseline), persistent fluid retention (symptoms of fluid retention are not tolerable after increasing the dose of the existing diuretic or the addition of a new diuretic), hemoglobin abnormalities (interruption for hemoglobin decrease from baseline of > 20 g/L; discontinuation for decrease in hemoglobin to < 80 g/L, a decrease in hemoglobin from baseline of > 50 g/L, need for transfusion), pregnancy, and liver aminotransferases abnormalities (interruption for aminotransferases ≥ 3 and $\leq 8 \times$ upper limit of normal (ULN); discontinuation for aminotransferases $> 8 \times$ ULN, aminotransferases $\geq 3 \times$ ULN and associated clinical symptoms of liver injury, or aminotransferases $\geq 3 \times$ ULN and associated increase in total bilirubin $\geq 2 \times$ ULN).

Compliance

The study inclusion criteria include an adherence provision for randomization. Subjects could be enrolled if they demonstrated $\geq 80\%$ compliance (pill counting) to study treatment (i.e., placebo) as well as $\geq 80\%$ compliance (pill counting) to the standardized background antihypertensive therapy during the RI period. Adherence was defined as number of tablets dispensed at visit (n) minus number of tablets returned at Visit (n +1) divided by the number of tablets that should have been taken during the period $\times 100$.

Between visits, adherence based on study treatment and the standardized background antihypertensive therapy accountability is expected to be at least 80%. Adherence values below 80% for the study treatment and/or the standardized background antihypertensive therapy without a medical justification (e.g., AE) after the randomization visit was considered a protocol deviation. In such cases, the Investigator was instructed to discuss and clarify the reasons for noncompliance with the subject and take appropriate actions to avoid re-occurrence. This discussion was to take place prior to providing the next study treatment to the subject.

Urine samples were collected throughout the study from initiation of the standardized background antihypertensive therapy and were analyzed for the presence of valsartan (one of the components of SBAT). The results of urine analysis from each visit were used to discuss the importance of study treatment intake with poorly adherent subjects.

Concomitant Medications

Treatments considered necessary for the subject's well-being and not categorized as forbidden concomitant medications were allowed during the study and must be documented in the medical charts.

The following therapies were allowed with the provision that they had been initiated and the dose stable at least 4 weeks prior to the screening visit and that the dose kept stable until the EOT: beta blockers, hormonal contraceptives, estrogen-replacement treatment, low dose acetylsalicylic acid for prevention of cardiovascular disease. In addition, the following therapies were allowed with the provision that they had been initiated at least 4 weeks prior to the screening visit and that the dose was kept stable until the end of DB part: nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors and anxiolytics.

Antihypertensive rescue medication was allowed in Part 2 and Part 3 according to local medical practice if, in the Investigator's opinion, the BP was not sufficiently controlled. Uncontrolled BP was confirmed via second measurement either at the next planned visit or at an unscheduled visit at the Investigator's discretion. In addition, adherence to the standardized background antihypertensive therapy was confirmed prior to initiating additional antihypertensive medication. Antihypertensive rescue medication was not allowed in the DB Part 1 of the study.

After Randomization, the dose of the existing diuretic (hydrochlorothiazide) could be increased, or a new diuretic could be added in the event of fluid retention as judged by the Investigator to be clinically relevant. The fluid retention was to be reported as an AE in the eCRF and fluid retention was to be reported as the indication for the diuretic. If the symptom(s) of fluid retention were not tolerable the subject was to discontinue the study treatment.

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The following concomitant therapies were forbidden from the screening visit until the EOT visit (any drug which may affect BP, except rescue and allowed medications described above), ERAs, or other investigational drugs.

Adverse Events of Special Interest

Adverse events of special interest were categorized as: hepatic disorders, anemia, edema / fluid retention, and decompensation / aggravation of heart failure.

Measures to Prevent Missing Data

A subject who prematurely discontinues study treatment was not considered as withdrawn from the study, provided that the subject's consent for this limited participation in the study had not been withdrawn. If a randomized subject discontinued study treatment, the subject was asked to perform the EOT visit (i.e., Visit 15) as soon as possible after the last dose of study treatment but, in any case, no later than 7 days and a safety FU visit 30 (+3) days thereafter. The main reason (e.g., AE, hypertension grade 3) was documented in the eCRF. Antihypertensive medication(s) were administered according to local standard-of-care at the Investigator's discretion. The standardized background antihypertensive therapy could be continued until the completion of the safety FU visit.

A subject who prematurely discontinued study treatment at any stage and withdrew consent to participate in any further study assessments was considered as withdrawn from the study. Subjects who died or were lost to follow-up were also considered as withdrawn from the study.

Subjects were considered as lost to follow-up if all reasonable attempts by the Investigator to communicate with the individual had failed. The site was instructed to take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted in the event the subject cannot be reached). If the subject could not be reached, the site was to make a reasonable effort to contact the subject, document all attempts (date, time and type of contact made), and enter the loss of follow-up information into the eCRF. The following methods were to be used: at least three attempts at contacts (e.g., telephone calls, or e-mails) must be placed to the last available telephone number or e-mail address, and one registered letter must be sent by post to the last available home address. Additional methods were considered acceptable if they were compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject was still unreachable after all contact attempts listed above, he/she was considered to be lost to follow-up. The reason for premature withdrawal from the study was recorded in the eCRF.

If for whatever reason (except death or loss-to-follow-up) a subject was withdrawn from the study, the Investigator made his/her best efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care.

16. Efficacy

Table 138. Additional Analyses for CKD Stage 1-2 (eGFR $\geq$ 60 mL/min/1.73 m²) Subgroup

Parameter	Aprocitentan 12.5 mg vs. Placebo	Aprocitentan 25 mg vs. Placebo
DB Part 1, FAS ¹		
SiSBP	-3.1 (-6.0, -0.3)	-1.3 (-4.1, 1.6)
SiDBP	-4.0 (-5.8, -2.2)	-3.5 (-5.3, -1.6)
24h ABPM SiSBP	-3.4 (-5.5, -1.2)	-5.0 (-7.1, -2.8)
24h ABPM SiDBP	-4.1 (-5.5, -2.7)	-5.6 (-7.1, -4.2)
DB-WD Part 3, mFAS ²		
SiSBP	-	-5.8 (-8.1, -3.5)
SiDBP	-	-4.9 (-6.5, -3.3)
24h ABPM SiSBP	-	-7.0 (-9.1, -4.8)
24h ABPM SiDBP	-	-6.5 (-7.9, -5.1)

Source: Statistical Reviewer Analysis; adsl.xpt, adbasc0.xpt, advsab.xpt

¹ LSM Difference to placebo (95% CI) in change from DB baseline at Week 4

² LSM Difference to placebo (95% CI) in change from DB-WD baseline at Week 40

Abbreviations: ABPM, ambulatory blood pressure monitoring; CI, confidence interval; CKD, chronic kidney disease; DB, double-blind; DB-WD, double-blind withdrawal; eGFR, estimated glomerular filtration rate; FAS, full analysis set; h, hour; LSM, least squares mean; mFAS, modified full analysis set; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure, vs., versus

17. Clinical Safety

Table 139. Listing of Treatment-Emergent Subject Deaths, Safety Population, PRECISION Study

Study Part	Study Treatment Arm	Subject ID	Age (Years)	Sex	Dosage (mg)	Dosing Duration (Days)	Study Day of Death	Cause of Death/ Preferred Term
<i>Study Part 1</i>								
	Aprocitentan 12.5 mg	ID-080A301-	(b) (6)	75 M	12.5	21	27	COVID-19 pneumonia
<i>Study Part 2</i>								
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	59 M	25	57	57	Sudden cardiac death
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	68 M	25	223	223	Death
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	64 F	25	203	213	Invasive breast carcinoma, brain oedema, subdural hemorrhage
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	77 M	25	201	207	Cerebrovascular accident
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	73 M	25	82	82	COVID-19 pneumonia
	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	79 M	25	32	32	Cerebrovascular accident
	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	65 M	25	44	51	COVID-19 pneumonia
	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	69 M	25	70	77	Procedural intestinal perforation
	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	73 F	25	87	107	COVID-19 pneumonia
<i>Study Part 3</i>								
	Aprocitentan 25 mg	ID-080A301-	(b) (6)	64 M	25	295	298	COVID-19 pneumonia, multiple organ dysfunction syndrome
<i>Safety Follow-Up Period</i>								
	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB)	ID-080A301-	(b) (6)	50 M	25	88	131	Respiratory failure, esophageal hemorrhage

Source: adae.xpt; Software: R; MedDRA Version: 24.1

Treatment-emergent death defined as occurring during treatment up to 30 days after last dose.

Abbreviations: COVID-19, coronavirus disease 2019; DB, double-blind; F, female; ID, identifier; M, male; SB, single-blind

Table 140. Subject Narratives for Treatment-Emergent Deaths Adjudicated as MACE, Safety Population, PRECISION Study

Subject ID	Narrative
(b) (6)	The 59-year-old White male experienced sudden death on Study Day 57. The subject began the study in the aprocitentan 12.5 mg arm and completed Part 1, switching to aprocitentan 25 mg for Part 2 on Study Day 33. On the morning of Day 57, the subject fainted, wheezed, and died. His wife called the ambulance, and emergency responders confirmed his death upon arrival. No diagnostic or treatment procedures were performed. Prior to the event, the subject's condition was reported as good, with no symptoms of fluid retention, and the subject's blood pressure was reported as 112/66 mmHg at the last visit on Day 46. Relevant medical conditions were reported as hypertension (9 years), previous cerebrovascular accident (7 years prior), myocardial ischemia, angina pectoris, chronic cardiac failure, supraventricular extrasystoles, type 2 diabetes mellitus, dyslipidemia, carotid arteriosclerosis, cerebral ischemia, and chronic pancreatitis. At baseline, he had a BMI of 30.5 kg/m² and an eGFR of 60 mL/min/1.73 m². Concomitant medications at baseline included: acetylsalicylic acid (100 mg daily), metformin (1000 mg twice daily), insulin human (30 IU twice daily), and atorvastatin (40 mg daily).
(b) (6)	The 68-year-old White male experienced death on Study Day 223. The subject began the study in the aprocitentan 12.5 mg arm and completed Part 1, switching to aprocitentan 25 mg for Part 2 on Study Day 29. On Day 253, the subject did not report to the scheduled visit and the site called to follow up. The wife stated the subject died during his sleep on Day 223. No autopsy was conducted. Prior to the event, the subject's blood pressure was reported as 145/62 mmHg at the last visit on Day 190. Relevant medical conditions were reported as hypertension (35 years), diabetes mellitus, dyslipidemia, hepatic steatosis, and sleep apnea syndrome. At baseline, he had a BMI of 35.7 kg/m² and an eGFR of 87 mL/min/1.73 m². Concomitant medications at baseline included: acetylsalicylic acid (100 mg daily.), metformin (850 mg three times daily), insulin human (dose unspecified), dapagliflozin (10 mg daily), dulaglutide (1.5 mg sq weekly), fenofibrate (200 mg daily) and atorvastatin (40 mg daily).
(b) (6)	The 64-year-old White female experienced infiltrative carcinoma in the left breast on Study Day 129 which led to the subject's death on Study Day 213. The subject began the study in the aprocitentan 12.5 mg arm and completed Part 1, switching to aprocitentan 25 mg for Part 2 on Study Day 31. The subject was diagnosed with breast cancer and began chemotherapy until Study Day 213 when she was hospitalized for an unspecified reason and died the same day. The primary cause of death was reported as invasive breast carcinoma. Autopsy revealed cerebral edema and subdural hemorrhage at the time of death. Relevant ongoing medical conditions at Screening included cardiac failure, coronary artery disease, myocardial fibrosis, breast neoplasm, hypercholesterolemia, cholecystitis chronic, pancreatitis chronic, and vascular encephalopathy. At baseline, she had a BMI of 34.2 kg/m² and an eGFR of 60 mL/min/1.73 m². Concomitant medications at baseline included: acetylsalicylic acid (100 mg daily) and rosuvastatin (20 mg daily).
(b) (6)	A 77-year-old White male experienced a fatal stroke on Study Day 207. The subject began the study in the aprocitentan 12.5 mg arm and completed Part 1, switching to aprocitentan 25 mg for Part 2 on Study Day 33. On the morning of Day 207, the subject was found in bed with "abrupt clinical signs of deep coma with noisy pathological breathing." Emergency responders confirmed death of the subject. The family doctor, who witnessed the subject's death, said to the relatives that he diagnosed the cause of death as stroke. An autopsy was not performed. The last available BP value on Day 201 was 128/70 mmHg. Ongoing medical conditions at Screening included angina pectoris, chronic cardiac failure, hypertensive heart disease, mitral valve disease, myocardial ischemia, dyslipidemia, chronic kidney disease, cerebral arteriosclerosis, and encephalopathy. At baseline, he had a BMI of 35.4kg/m² and an eGFR of 44 mL/min/1.73 m². Concomitant medications at baseline included rosuvastatin (10 mg daily).

(b) (6)

A 79-year-old White male experienced left middle cerebral artery stroke resulting in hospitalization on Study Day 32, and death on Study Day 37. The subject began the study in the aprocitentan 25 mg arm and completed Part 1, starting Part 2 on Study Day 29. On Study Day 31, the subject was reported as normal by his wife. The next day, she found him on the bathroom floor, and he was taken to the emergency department 12 hours later, presenting with right-sided weakness, the inability follow commands, and aphasia. Tissue plasminogen activator was not administered due to being outside the treatment time criteria. Hemoglobin and hematocrit were within normal ranges, eGFR was stable at 50 mL/min/1.73 m². On the same day, the subject was transferred to another hospital for possible mechanical thrombectomy, which ultimately was not attempted due to the core infarct being too large, and expiration of the treatment time window. The subject was then discharged to palliative care on Study Day 35 and died on Study Day 37. The last available BP value on Day 26 was 124/72 mmHg. Ongoing medical conditions at Screening included chronic kidney disease, aortic arteriosclerosis, peripheral edema, sleep apnea syndrome, peripheral venous disease, gastroesophageal reflux disease, and hyperparathyroidism. At baseline, he had a BMI of 36.6 kg/m² and an eGFR of 47 mL/min/1.73 m². Concomitant medications at baseline included acetylsalicylic acid (81 mg daily), omeprazole (20 mg daily), and montelukast sodium (10 mg daily).

Source: PRECISION CSR, Subject Narratives, and Clinical Report Forms

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate, ID, identifier; MACE, major adverse cardiovascular events

Table 141. Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, PRECISION Study, Part 2 (Week 4 to 36)

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB) N=232 n (%)	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Placebo (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Combined Aprocitentan 25 mg (SB) N=704 n (%)
AE leading to permanent discontinuation of study drug	6 (2.6)	9 (3.8)	12 (5.1)	27 (3.8)
Cardiac disorders (SOC)				
Acute coronary syndrome (FMQ)	1 (0.4)	0	1 (0.4)	2 (0.3)
Angina unstable	1 (0.4)	0	0	1 (0.1)
Myocardial infarction	0	0	1 (0.4)	1 (0.1)
Myocardial ischemia (FMQ)	1 (0.4)	0	1 (0.4)	2 (0.3)
Angina unstable	1 (0.4)	0	0	1 (0.1)
Myocardial infarction	0	0	1 (0.4)	1 (0.1)
Heart failure (FMQ)	0	0	2 (0.8)	2 (0.3)
Cardiac failure chronic	0	0	1 (0.4)	1 (0.1)
Cardiac failure congestive	0	0	1 (0.4)	1 (0.1)
Myocardial infarction (FMQ)	0	0	1 (0.4)	1 (0.1)
Myocardial infarction	0	0	1 (0.4)	1 (0.1)

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System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB) N=232 n (%)	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Placebo (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Combined Aprocitentan 25 mg (SB) N=704 n (%)
Gastrointestinal disorders (SOC)				
Dry mouth (FMQ)	0	1 (0.4)	0	1 (0.1)
Dry mouth	0	1 (0.4)	0	1 (0.1)
General disorders and administration site conditions (SOC)				
Peripheral edema (FMQ)	1 (0.4)	0	2 (0.8)	3 (0.4)
Oedema peripheral	1 (0.4)	0	2 (0.8)	3 (0.4)
Hepatobiliary disorders (SOC)				
Hepatic injury (FMQ)	0	0	1 (0.4)	1 (0.1)
Alanine aminotransferase increased	0	0	1 (0.4)	1 (0.1)
Infections and infestations (SOC)				
Nasopharyngitis (FMQ)	0	0	1 (0.4)	1 (0.1)
Vasomotor rhinitis	0	0	1 (0.4)	1 (0.1)
Viral Infection (FMQ)	0	2 (0.8)	1 (0.4)	3 (0.4)
COVID-19 pneumonia	0	2 (0.8)	1 (0.4)	3 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)				
Malignancy (FMQ)	0	1 (0.4)	0	1 (0.1)
Metastatic neoplasm	0	1 (0.4)	0	1 (0.1)
Nervous system disorders (SOC)				
Dysgeusia (FMQ)	0	1 (0.4)	0	1 (0.1)
Dysgeusia	0	1 (0.4)	0	1 (0.1)
Stroke and TIA (FMQ)	0	1 (0.4)	0	1 (0.1)
Cerebrovascular accident	0	1 (0.4)	0	1 (0.1)
Syncope (FMQ)	0	0	1 (0.4)	1 (0.1)
Syncope	0	0	1 (0.4)	1 (0.1)
Renal and urinary disorders (SOC)				
Acute kidney injury (FMQ)	0	1 (0.4)	0	1 (0.1)
Acute kidney injury	0	1 (0.4)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders (SOC)				
Dyspnea (FMQ)	1 (0.4)	0	0	1 (0.1)
Dyspnoea	1 (0.4)	0	0	1 (0.1)
Respiratory failure (FMQ)	1 (0.4)	0	0	1 (0.1)
Respiratory failure	1 (0.4)	0	0	1 (0.1)

System Organ Class FMQ (Narrow) Preferred Term	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB) N=232 n (%)	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Placebo (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Combined Aprocitentan 25 mg (SB) N=704 n (%)
Skin and subcutaneous tissue disorders (SOC)				
Rash (FMQ)	0	0	1 (0.4)	1 (0.1)
Dermatitis allergic	0	0	1 (0.4)	1 (0.1)
Vascular disorders (SOC)				
Thrombosis (FMQ)	1 (0.4)	0	1 (0.4)	2 (0.3)
Angina unstable	1 (0.4)	0	0	1 (0.1)
Myocardial infarction	0	0	1 (0.4)	1 (0.1)
Thrombosis arterial (FMQ)	1 (0.4)	0	1 (0.4)	2 (0.3)
Angina unstable	1 (0.4)	0	0	1 (0.1)
Myocardial infarction	0	0	1 (0.4)	1 (0.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 2 up to the day before the start date of Part 3 (or EOT+30 days if the subject did not enter Part 3).

Duration is median 32 weeks (minimum 0.1, maximum 37.7 weeks).

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; DB, double-blind; EOT, end of treatment; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SB, single-blind; SOC, system organ class; TIA, transient ischemic attack

Table 142. Adverse Events of Edema (Grouped Query) by Demographic Subgroup, Safety Population, PRECISION Study, Part 1, Double-Blind Period (Weeks 0 to 4)

Characteristic	Aprocitentan 12.5 mg N=243 n/N_s (%)	Aprocitentan 25 mg N=245 n/N_s (%)	Placebo N=242 n/N_s (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
Sex, n (%)					
Female	10/99 (10.1)	15/98 (15.3)	2/99 (2.0)	8.1 (1.5, 14.6)	13.3 (5.6, 20.9)
Male	12/144 (8.3)	29/147 (19.7)	3/143 (2.1)	6.2 (1.1, 11.3)	17.6 (10.8, 24.5)
Age group, years, n (%)					
18 to <65	6/143 (4.2)	22/138 (15.9)	2/128 (1.6)	2.6 (-1.3, 6.6)	14.4 (7.9, 20.9)
65 to <85	16/100 (16.0)	22/107 (20.6)	3/114 (2.6)	13.4 (5.6, 21.1)	17.9 (9.7, 26.1)
Age group, years, n (%)					
≥75	4/22 (18.2)	8/22 (36.4)	1/28 (3.6)	14.6 (-2.9, 32.1)	32.8 (11.5, 54.0)

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Characteristic	Aprocitentan 12.5 mg N=243 n/N_s (%)	Aprocitentan 25 mg N=245 n/N_s (%)	Placebo N=242 n/N_s (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
Race, n (%)					
Asian	1/11 (9.1)	2/14 (14.3)	0/13 (0)	9.1 (-7.9, 26.1)	14.3 (-4.0, 32.6)
Black or African American	0/28 (0)	3/29 (10.3)	0/25 (0)	0 (0, 0)	10.3 (-0.7, 21.4)
Native Hawaiian or Other Pacific Islander	1/1 (100)	0/0 (NA)	0/0 (NA)	NA	NA
Not reported	0/0 (NA)	1/1 (100)	0/2 (0)	NA	100.0 (-31.5, 100.0)
Other	0/0 (NA)	0/0 (NA)	0/1 (0)	NA	NA
White	20/203 (9.9)	38/201 (18.9)	5/201 (2.5)	7.4 (2.7, 12.0)	16.4 (10.6, 22.2)
Ethnicity, n (%)					
Hispanic or Latino	2/28 (7.1)	0/22 (0)	1/23 (4.3)	2.8 (-9.9, 15.5)	-4.3 (-12.7, 4.0)
Not Hispanic or Latino	20/213 (9.4)	43/221 (19.5)	4/216 (1.9)	7.5 (3.2, 11.8)	17.6 (12.1, 23.1)
Not reported	0/1 (0)	1/1 (100)	0/3 (0)	0 (0, 0)	100.0 (-12.3, 100.0)
Unknown	0/1 (0)	0/1 (0)	0/0 (NA)	NA	NA
Is in United States, n (%)					
United States	2/68 (2.9)	9/76 (11.8)	1/67 (1.5)	1.4 (-3.5, 6.4)	10.3 (2.5, 18.2)
Non-United States	20/175 (11.4)	35/169 (20.7)	4/175 (2.3)	9.1 (3.9, 14.4)	18.4 (11.9, 24.9)
BMI category (kg/m²) at screening					
<25.0	1/10 (10.0)	0/11 (0)	1/15 (6.7)	3.3 (-19.1, 25.8)	-6.7 (-19.3, 6.0)
25.0 to <30.0	4/65 (6.2)	12/60 (20.0)	0/63 (0)	6.2 (0.3, 12.0)	20.0 (9.9, 30.1)
30.0 to <40.0	16/135 (11.9)	24/132 (18.2)	3/132 (2.3)	9.6 (3.6, 15.6)	15.9 (8.9, 23.0)
≥40.0	1/33 (3.0)	8/42 (19.0)	1/32 (3.1)	-0.1 (-8.5, 8.3)	15.9 (2.6, 29.2)
Any selected AHT stopped at screening, n (%)					
Yes	6/52 (11.5)	10/62 (16.1)	1/48 (2.1)	9.5 (-0.1, 19.0)	14.0 (4.0, 24.1)
No	16/191 (8.4)	34/183 (18.6)	4/194 (2.1)	6.3 (1.9, 10.7)	16.5 (10.5, 22.5)
Baseline eGFR, mL/min/1.73 m², n (%)					
<30	1/8 (12.5)	0/7 (0)	0/6 (0)	12.5 (-10.4, 35.4)	0 (0, 0)
30 to <45	5/17 (29.4)	6/21 (28.6)	1/10 (10.0)	19.4 (-9.1, 48.0)	18.6 (-8.2, 45.4)
45 to <60	4/30 (13.3)	8/34 (23.5)	0/29 (0)	13.3 (1.2, 25.5)	23.5 (9.3, 37.8)
≥60	12/188 (6.4)	30/183 (16.4)	4/197 (2.0)	4.4 (0.3, 8.4)	14.4 (8.6, 20.1)
Prior history of heart failure, n (%)					
Heart failure	5/48 (10.4)	12/50 (24.0)	2/43 (4.7)	5.8 (-4.9, 16.5)	19.3 (5.9, 32.8)
Dose of amlodipine at baseline, n (%)					
Amlodipine 5 mg	5/79 (6.3)	6/61 (9.8)	1/72 (1.4)	4.9 (-1.1, 11.0)	8.4 (0.5, 16.4)
Amlodipine 10 mg	17/164 (10.4)	38/184 (20.7)	4/170 (2.4)	8.0 (2.8, 13.2)	18.3 (12.0, 24.6)

Characteristic	Aprocitentan 12.5 mg N=243 n/N _s (%)	Aprocitentan 25 mg N=245 n/N _s (%)	Placebo N=242 n/N _s (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
Loop diuretic at screening, n (%)					
Yes	4/30 (13.3)	5/41 (12.2)	1/36 (2.8)	10.6 (-2.7, 23.9)	9.4 (-1.9, 20.8)
No	18/213 (8.5)	39/204 (19.1)	4/206 (1.9)	6.5 (2.3, 10.7)	17.2 (11.5, 22.9)
More than 1 diuretic at screening, n (%)					
Yes	2/27 (7.4)	4/31 (12.9)	1/26 (3.8)	3.6 (-8.8, 15.9)	9.1 (-4.9, 23.0)
No	20/216 (9.3)	40/214 (18.7)	4/216 (1.9)	7.4 (3.1, 11.7)	16.8 (11.3, 22.4)

Source: adae.xpt, adsl.xpt, admh.xpt, and adcm.xpt; Software: R

Edema (GQ) contains: Fluid retention, oedema peripheral, face oedema, pulmonary oedema, localised oedema.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

"Any selected AHT stopped at screening" specifically refers to the medications eplerenone, spironolactone, furosemide, torsemide and metolazone.

Abbreviations: AHT; antihypertensive therapy; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; vs., versus

Table 143. Adverse Events Assessment of Edema (Grouped Query) Safety Population, PRECISION Study, Part 2, Single-Blind Period (Weeks 4 to 36)

Adverse Events Assessment Preferred Term	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB) N=232 n (%)	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Placebo (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Combined Aprocitentan 25 mg (SB) N=704 n (%)
Edema (GQ)	37 (15.9)	29 (12.3)	53 (22.5)	119 (16.9)
Face oedema	0	0	2 (0.8)	2 (0.3)
Fluid retention	8 (3.4)	3 (1.3)	10 (4.2)	21 (3.0)
Localised oedema	0	1 (0.4)	2 (0.8)	3 (0.4)
Oedema peripheral	29 (12.5)	26 (11.0)	40 (16.9)	95 (13.5)
Pulmonary oedema	1 (0.4)	0	1 (0.4)	2 (0.3)
Maximum severity				
Death	0	0	0	0
Life-threatening	0	0	0	0
Severe	0	0	2 (0.8)	2 (0.3)
Moderate	13 (5.6)	5 (2.1)	21 (8.9)	39 (5.5)
Mild	24 (10.3)	24 (10.2)	30 (12.7)	78 (11.1)
Serious	0	0	1 (0.4)	1 (0.1)
Deaths	0	0	0	0
Resulting in discontinuation	1 (0.4)	0	3 (1.3)	4 (0.6)

Adverse Events Assessment Preferred Term	Aprocitentan 12.5 mg (DB) to Aprocitentan 25 mg (SB) N=232 n (%)	Aprocitentan 25 mg (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Placebo (DB) to Aprocitentan 25 mg (SB) N=236 n (%)	Combined Aprocitentan 25 mg (SB) N=704 n (%)
Resulting in hospitalization	0	0	1 (0.4)	1 (0.1)
Relatedness	17 (7.3)	10 (4.2)	24 (10.2)	51 (7.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any AE with an onset date between the start date of Part 2 up to the day before the start date of Part 3 (or EOT +30 days if the subject did not enter Part 3).

Duration is median 32 weeks (minimum 0.1, maximum 37.7 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Relatedness is determined by investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; EOT, end of treatment; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 144. Narratives for Adjudicated MACE and MACE-Plus, Safety Population, PRECISION Study

Subject ID	Clinical Information
<i>Part 1</i>	
(b) (6)	The 77-year-old White male in the aprocitentan 12.5 mg arm experienced nonfatal ischemic stroke on Study Day 27. The subject was hospitalized due to sudden dysarthria. A brain CT showed the presence of a hypodense area with blurry borders in the area of mesencephalon at the left side towards thalamus, which correspond to subacute ischemic changes. Otherwise, there was no intracranial bleeding or expansive process. An MRI was not performed. The study drug was permanently discontinued on Day 28 due to ischemic stroke. The event remained unresolved and was assessed as related to the study drug. Relevant medical conditions were reported as hypertension, previous transient ischemic attack, type 2 diabetes mellitus, dyslipidemia, and CKD. At baseline, he had a BMI of 29.7 kg/m ² , eGFR of 38 mL/min/1.73 m ² , and NT-proBNP of 246 pg/mL.
(b) (6)	The 75-year-old White female in the aprocitentan 12.5 mg arm experienced an SAE of subacute right medial occipital lobe infarct on Study Day 17. The subject noticed symptoms of floaters in both eyes but did not notify the site. On Study Day 48, an MRI of the head without contrast indicated probable late subacute infarct in the right medial occipital lobe, noted to be at least several weeks in age, which corresponded with the onset of her visual changes. There was no evidence of hemorrhage or recent infarct. The study drug was interrupted from Day 38-41. The event remained unresolved and was considered not related to the study drug. The subject restarted treatment on Study Day 41 and completed Part 2 and Part 3 of the study. Relevant medical conditions were reported as hypertension (40 years) and peripheral edema. At baseline, she had a BMI of 31 kg/m ² and an eGFR of 62 mL/min/1.73 m ² .
(b) (6)	The 72-year-old White male in the aprocitentan 12.5 mg arm experienced a serious event of nonfatal myocardial infarction on Study Day 19-23. The event resolved with treatment. No action with study drug was taken. The event was assessed as not related. On Study Day 95, the subject experienced a serious event of nonfatal myocardial infarction related to coronary artery bypass graft (CABG) surgery, which was performed the day prior. The event resolved with coronarography and bypass. No action with study drug was taken. The event was assessed as not related. Relevant ongoing medical conditions at Screening included chronic cardiac failure, angina, coronary artery disease, myocardial ischemia, hypercholesterolemia, peripheral

Subject ID	Clinical Information
(b) (6)	arterial occlusive disease, diabetic nephropathy, and diabetes. At baseline, he had a BMI of 32.7 kg/m ² and an eGFR of 60 mL/min/1.73 m ² .
(b) (6)	A 56-year-old White male in the aprocitentan 25 mg arm experienced a serious event of nonfatal stroke on Study Day 4-23. The event resolved with sequelae (speech impaired and memory reduced). The study drug was permanently discontinued on Study Day 15. The event was assessed as not related. Ongoing medical conditions at Screening included type 2 diabetes, dyslipidemia, and tobacco use. At baseline, he had a BMI of 35.9kg/m ² and an eGFR of 100 mL/min/1.73 m ² .
(b) (6)	A 67-year-old White male in the aprocitentan 25 mg arm experienced an SAE of pulmonary edema, cardiac failure, and increased blood pressure on Study Day 8-12. The subject was admitted to the hospital with a diagnosis of heart failure with preserved ejection fraction (HFpEF) with flash pulmonary edema after experiencing increasing dyspnea. Blood pressure upon arrival was 220/104 mmHg and chest X-ray showed early pulmonary edema. The subject's NT-proBNP value during hospitalization was not reported. The subject recovered after treatment and the event was considered not related to the study drug. There was no action take with study treatment. On Study Day 23, the subject presented to the emergency department with severe chest pain and peripheral edema that resolved after treatment with transdermal nitroglycerin and furosemide. There was no action taken with study treatment and the event was considered not related to the study drug. Ongoing medical conditions at Screening included type 2 diabetes, dyslipidemia, history of transient ischemic attack, and peripheral edema. At baseline, he had a BMI of 38.1kg/m ² and an eGFR of 62 mL/min/1.73 m ² .
(b) (6)	An 83-year-old White female in the aprocitentan 25 mg arm had an SAE of cardiac failure on Study Day 22-30. The subject was admitted to the hospital with a diagnosis of worsening of chronic heart failure after experiencing edema and dyspnea since study Day 11. The study drug was interrupted from Day 22-30 and restarted on Day 31. The subject recovered after treatment and the event was considered not related to the study drug. Ongoing medical conditions at Screening included atrial fibrillation, chronic heart failure, chronic kidney disease, type 2 diabetes, dyslipidemia, transient ischemic attack, and peripheral arterial occlusive disease. At baseline, she had a BMI of 37.1kg/m ² and an eGFR of 38 mL/min/1.73 m ² .
Part 2	
(b) (6)	The 66-year-old Black male in the aprocitentan 25 mg arm experienced a serious event of nonfatal myocardial infarction on Study Day 41. The subject was hospitalized with a diagnosis of myocardial infarction of mild intensity (non-ST-elevation) after reporting edema, dyspnea, and chest pain for the prior 4 days. The event resolved after treatment. The study drug was permanently discontinued on Study Day 41. The event was assessed as not related. Relevant ongoing medical conditions at Screening included coronary artery disease, left bundle branch block, hypercholesterolemia, peripheral arterial occlusive disease, diabetic nephropathy, and type 2 diabetes. At baseline, he had a BMI of 30.3 kg/m ² and an eGFR of 72 mL/min/1.73 m ² .
(b) (6)	The 73-year-old White male in the aprocitentan 25 mg arm experienced a serious event of nonfatal myocardial infarction on Study Day 181 during hospitalization for a scheduled left femoral thromboendarterectomy of moderate intensity and iliac stenting. He was transferred to the cardiology unit and underwent a coronarography on Day 186 that revealed trivascular coronaropathy with occlusion of medio-proximal anterior interventricular artery. The same day, he underwent a coronary angioplasty plus stent, on common trunk and distal segment. The procedure was uncomplicated and regular; the subject was discharged on study Day 190. No action was taken with the study drug and the event was assessed as not related to study treatment. Relevant ongoing medical conditions at Screening included hypercholesterolemia, chronic kidney disease, peripheral vascular disorder, and type 2 diabetes. At baseline, he had a BMI of 27.8 kg/m ² and an eGFR of 30 mL/min/1.73 m ² .

Subject ID	Clinical Information
(b) (6)	A 57-year-old Black male in the aprocitentan 25 mg arm had an SAE of congestive heart failure exacerbation on Study Day 46-75. The subject was admitted to the hospital on Study Day 68 with a diagnosis of congestive heart failure exacerbation after experiencing a three-week history of increasing dyspnea, peripheral edema, and cough. The subject recovered after treatment and the event was considered not related to the study drug. During hospitalization on study Day 68, the subject experience acute kidney failure of moderate intensity, which was assessed as related to study treatment. The study drug was permanently discontinued the same day. Ongoing medical conditions at Screening included chronic left ventricular failure, type 2 diabetes, dyslipidemia, chronic kidney disease, diabetic retinopathy, and peripheral edema. At baseline, he had a BMI of 42.9kg/m ² and an eGFR of 59 mL/min/1.73 m ² .
(b) (6)	A 66-year-old White female in the aprocitentan 25 mg arm experienced an SAE of congestive heart failure on Study Day 39-47. The subject was admitted to the hospital on Study Day 39 after experiencing a two-day history of dyspnea. Chest CTA showed bilateral pleural effusion and pulmonary edema secondary to heart failure. There was no pulmonary embolism or signs of infiltrates. On Day 41, transthoracic echocardiogram showed an ejection fraction of 50-55% with grade 3/4 diastolic dysfunction and right ventricular systolic pressure of 51 mmHg. A nuclear stress test showed an intermediate risk stress test due to left ventricular dilatation and transient ischemic dilatation, most consistent with either a dilated cardiomyopathy or could be seen with multivessel coronary disease and balanced ischemia. The subject recovered after treatment and the event was assessed as not related to the study drug. The study drug was permanently discontinued on study Day 39. Ongoing medical conditions at Screening included left ventricular hypertrophy, type 2 diabetes, and dyslipidemia. At baseline, he had a BMI of 34.6 kg/m ² and an eGFR of 91 mL/min/1.73 m ² .
(b) (6)	A 70-year-old White male in the aprocitentan 25 mg arm experienced an SAE of heart failure on Study Day 53-55. The subject was admitted to the hospital on Study Day 53 after experiencing a 2-week history of dyspnea and peripheral edema. A 2D echocardiogram revealed a serious event of grade 2 left ventricular diastolic dysfunction of moderate intensity with preserved ejection fraction. The subject recovered after treatment and the event was assessed as not related to the study drug. No action was taken with the study treatment. Of note, the hospitalization was complicated by diagnosis of COVID-19 of severe intensity and the subject remained in the hospital until Study Day 63. Ongoing medical conditions at Screening included chronic kidney disease, coronary artery disease, type 2 diabetes, and dyslipidemia. At baseline, he had a BMI of 26.7 kg/m ² and an eGFR of 37 mL/min/1.73 m ² .
(b) (6)	A 72-year-old Black male in the aprocitentan 25 mg arm experienced an SAE of pulmonary edema, congestive heart failure, and hypertensive urgency on Study Day 134 to 137 that led to drug interruption for the hypertensive urgency. The subject was admitted to the hospital with a diagnosis of congestive heart failure, pulmonary edema in the setting of hypertensive urgency, acute kidney injury on chronic kidney disease, and atrial flutter. Blood pressure upon arrival was reported as 209/60 mmHg and chest X-ray showed enlarged cardiac silhouette and pulmonary vasculature congestion. The subject recovered after treatment with intravenous (IV) furosemide, nitrates, and hydralazine. The study treatment was interrupted on Day 137 due to the hypertensive urgency. The event was considered not related to study drug. Prior to the study (at screening), the subject's individual background antihypertensive therapy included SBAT and hydralazine (50 mg twice daily) which was discontinued at that time, per study protocol. The subject was restarted on study treatment on Study Day 147, completing the study Parts 2 and 3 in the aprocitentan 25 mg arm as scheduled.
(b) (6)	A 79-year-old White female in the aprocitentan 25 mg arm experienced an SAE of cardiac failure on Study Day 151-157. The subject was admitted to the hospital on Study Day 151 after experiencing a 4-week history of night dyspnea and peripheral

Subject ID	Clinical Information
Part 3	edema. Blood pressure was 154/102 mmHg. Chest X-ray showed signs of congestion in the small circulation, veil-shaped reduction in transparency on both sides in the lower lung fields of fluido-thorax nature. The subject recovered after treatment and the event was assessed as not related to the study drug due to two recent episodes of viral respiratory infection which exacerbated her heart failure. No action was taken with the study treatment. Ongoing medical conditions at Screening included cardiac failure, peripheral edema, chronic kidney disease, coronary artery disease, type 2 diabetes, history of ischemic stroke, and dyslipidemia. At baseline, she had a BMI of 46.1 kg/m² and an eGFR of 33 mL/min/1.73 m².
(b) (6)	A 63-year-old White male in the aprocitentan 25 mg arm experienced a serious event of nonfatal myocardial infarction on Study Day 360-371. The subject was hospitalized with a diagnosis of myocardial infarction (type 1 with ST segment elevation) and cardiogenic shock after a 3-day history of chest pain and irregular heartbeat. No action was taken with the study drug and the event was assessed as not related to study treatment. Relevant ongoing medical conditions at Screening included left ventricular hypertrophy, cerebral ischemia, and hypercholesterolemia. At baseline, he had a BMI of 36.3 kg/m² and an eGFR of 80 mL/min/1.73 m².
(b) (6)	A 63-year-old White male in the aprocitentan 25 mg arm experienced an SAE of unstable angina and aortic stenosis on Study Day 312-332. The subject was admitted to the hospital on Study Day 313 after experiencing chest pain. Coronary angiography showed evidence of normal coronary vessels. Echocardiography revealed worsened aortic stenosis on native bicuspid valve, maximum gradient >80 mmHg, with surgical indication. The subject recovered after aortic valve replacement and the event was assessed as not related to the study drug. Study treatment was permanently discontinued on Study Day 312. Ongoing medical conditions at Screening included cardiac failure, peripheral edema, chronic kidney disease, coronary artery disease, type 2 diabetes, history of ischemic stroke, and dyslipidemia. At baseline, he had a BMI of 46.1 kg/m² and an eGFR of 33 mL/min/1.73 m².
(b) (6)	A 75-year-old White male in the aprocitentan 25 mg arm experienced an SAE of acute diastolic heart failure on Study Day 315-317. The subject was admitted to the hospital on Study Day 315 for volume overload with mild pulmonary edema and lower extremity edema after experiencing a 10-day history of mild peripheral edema. Chest X-ray showed signs of congestion with small pleural effusions. A second local B-natriuretic peptide (Day 136) was 217 pg/mL. Echocardiography revealed mildly dilated right atrium and increased left atrial volume and volume index; a trace to mild degree of mitral regurgitation; mild pulmonary hypertension with estimated right ventricular systolic pressure of 40 mmHg. CT pulmonary angiogram showed no acute pulmonary embolism, minimal interstitial edema, trace bilateral pleural effusions. The subject recovered after treatment and the event was assessed as not related to the study drug. No action was taken with the study treatment. Ongoing medical conditions at Screening included type 2 diabetes and dyslipidemia. At baseline, he had a BMI of 34.3 kg/m² and an eGFR of 87 mL/min/1.73 m².

Subject ID	Clinical Information
(b) (6)	A 62-year-old White male in the aprocitentan 25 mg arm experienced an SAE of dyspnea on Study Day 277-282. The subject was admitted to the hospital on Study Day 277 for fluid retention and decompensation of heart failure. The subject was previously diagnosed with pulmonary neoplasm and was taking chemotherapy at the time of hospitalization. The subject recovered from the dyspnea and heart failure exacerbation after treatment and the event was assessed as not related to the study drug. The study treatment had already been permanently discontinued prior to the event on Study Day 276. Ongoing medical conditions at Screening included cardiac failure, type 2 diabetes and dyslipidemia. At baseline, he had a BMI of 32.2 kg/m ² and an eGFR of 91 mL/min/1.73 m ² .

Source: PRECISION CSR, Subject Narratives, and Clinical Report Forms

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CT, computed tomography; CTA, computed tomography angiography; eGFR, estimated glomerular filtration rate; HFpEF, Heart failure with preserved ejection fraction; IV, intravenous; MACE, major adverse cardiac event; MACE-Plus, major adverse cardiac event plus heart failure and thromboembolic events, MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro b-type natriuretic peptide; SAE, serious adverse event; SBAT, standard background antihypertensive therapy; 2D, two-dimensional

Table 145. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, PRECISION Study

Laboratory Parameter	Aprocitentan 12.5 mg N=243 n/N _w (%)	Aprocitentan 25 mg N=245 n/N _w (%)	Placebo N=242 n/N _w (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	<i>Study Part 1</i>				
Hemoglobin, low (g/dL)					
Level 2 (>1.5 g/dL dec. from baseline)	30/211 (14.2)	36/215 (16.7)	5/213 (2.3)	11.9 (6.7, 17.0)	14.4 (9.0, 19.8)
Level 3 (>2 g/dL dec. from baseline)	14/211 (6.6)	7/215 (3.3)	2/213 (0.9)	5.7 (2.1, 9.3)	2.3 (-0.4, 5.0)
Decrease from baseline to below 10.0 g/dL	7/211 (3.3)	4/215 (1.9)	0/213 (0)	3.3 (0.8, 6.7)	1.9 (-0.2, 4.7)
<i>Study Part 2</i>					
Hemoglobin, low (g/dL)					
Level 2 (>1.5 g/dL dec. from baseline ¹)	95/230 (41.3)	97/233 (41.6)	112/233 (48.1)	304/696 (43.7)	
Level 3 (>2 g/dL dec. from baseline ¹)	46/230 (20.0)	38/233 (16.3)	55/233 (23.6)	139/696 (20.0)	
<i>Study Part 3</i>					
Hemoglobin, low (g/dL)					
Level 2 (>1.5 g/dL dec. from baseline ²)		13/309 (4.2)	4/300 (1.3)		2.9 (0.3, 5.5)
Level 3 (>2 g/dL dec. from baseline ²)		9/309 (2.9)	2/300 (0.7)		2.2 (0.2, 4.3)

Laboratory Parameter	Aprocitentan 12.5 mg N=243 n/N _w (%)	Aprocitentan 25 mg N=245 n/N _w (%)	Placebo N=242 n/N _w (%)	Aprocitentan 12.5 mg vs. Placebo Risk Difference (%) (95% CI)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	Hemoglobin, high (g/dL)				
Level 2 (>2 g/dL inc. from baseline ²)		15/309 (4.9)	44/300 (14.7)		-9.8 (-14.5, -5.1)
Level 3 (>3 g/dL inc. from baseline ²)		1/309 (0.3)	3/300 (1.0)		-0.7 (-2.0, 0.6)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is median 4 weeks (minimum 0.1, maximum 9.7 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

¹ Baseline was end of Part 1 value

² Baseline was end of Part 2 value

Abbreviations: CI, confidence interval; dec., decreased; inc., increased; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; vs., versus

Table 146. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, PRECISION Study, Part 3 Double-Blind Withdrawal Period (Weeks 36 to 48)

Laboratory Parameter	Aprocitentan 25 mg N=310 n/N _w (%)	Placebo N=303 n/N _w (%)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
	Potassium, low (mEq/L)		
Level 1 (<3.6)	46/309 (14.9)	43/300 (14.3)	0.6 (-5.1, 6.2)
Level 2 (<3.4)	15/309 (4.9)	16/300 (5.3)	-0.5 (-4.0, 3.0)
Level 3 (<3)	2/309 (0.6)	4/300 (1.3)	-0.7 (-2.3, 0.9)
Potassium, high (mEq/L)			
Level 1 (>5.5)	12/309 (3.9)	16/300 (5.3)	-1.4 (-4.8, 1.9)
Level 2 (>6)	4/309 (1.3)	1/300 (0.3)	1.0 (-0.5, 2.4)
Level 3 (>6.5)	1/309 (0.3)	1/300 (0.3)	-0.0 (-0.9, 0.9)
Protein, total, low (g/dL)			
Level 1 (<6)	10/309 (3.2)	4/300 (1.3)	1.9 (-0.5, 4.3)
Level 2 (<5.4)	0/309 (0)	0/300 (0)	0 (0, 0)
Level 3 (<5)	0/309 (0)	0/300 (0)	0 (0, 0)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	8/309 (2.6)	7/300 (2.3)	0.3 (-2.2, 2.7)
Level 2 (≥2X baseline)	3/309 (1.0)	2/300 (0.7)	0.3 (-1.1, 1.7)
Level 3 (≥3X baseline)	2/309 (0.6)	0/300 (0)	0.6 (-0.2, 1.5)

NDA 217686
TRYVIO (aprocitentan)

Laboratory Parameter	Aprocitentan 25 mg N=310 n/N _w (%)	Placebo N=303 n/N _w (%)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
eGFR, low (ml/min/1.73 m ²)			
Level 1 (≥25% decrease)	31/309 (10.0)	23/300 (7.7)	2.4 (-2.1, 6.9)
Level 2 (≥50% decrease)	5/309 (1.6)	2/300 (0.7)	1.0 (-0.7, 2.6)
Level 3 (≥75% decrease)	1/309 (0.3)	0/300 (0)	0.3 (-0.3, 1.0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is median 11.9 weeks (minimum 0.6, maximum 15.3 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; vs., versus

Table 147. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, PRECISION Study, Part 3 Double-Blind Withdrawal Period (Weeks 36 to 48)

Laboratory Parameter	Aprocitentan 25 mg N=310 n/N _w (%)	Placebo N=303 n/N _w (%)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	134/309 (43.4)	154/300 (51.3)	-8.0 (-15.9, -0.1)
Level 2 (>210)	108/309 (35.0)	130/300 (43.3)	-8.4 (-16.1, -0.7)
Level 3 (>225)	79/309 (25.6)	105/300 (35.0)	-9.4 (-16.7, -2.2)
HDL, males, low (mg/dL)			
Level 1 (<40)	106/186 (57.0)	98/179 (54.7)	2.2 (-7.9, 12.4)
Level 2 (<30)	25/186 (13.4)	23/179 (12.8)	0.6 (-6.3, 7.5)
Level 3 (<20)	0/186 (0)	2/179 (1.1)	-1.1 (-2.7, 0.4)
HDL, females, low (mg/dL)			
Level 1 (<50)	72/123 (58.5)	63/121 (52.1)	6.5 (-6.0, 18.9)
Level 2 (<40)	38/123 (30.9)	18/121 (14.9)	16.0 (5.7, 26.4)
Level 3 (<20)	0/123 (0)	0/121 (0)	0 (0, 0)
LDL, high (mg/dL)			
Level 1 (>130)	90/304 (29.6)	120/295 (40.7)	-11.1 (-18.7, -3.5)
Level 2 (>160)	37/304 (12.2)	60/295 (20.3)	-8.2 (-14.1, -2.3)
Level 3 (>190)	10/304 (3.3)	22/295 (7.5)	-4.2 (-7.8, -0.6)

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Laboratory Parameter	Aprocitentan 25 mg N=310 n/N _w (%)	Placebo N=303 n/N _w (%)	Aprocitentan 25 mg vs. Placebo Risk Difference (%) (95% CI)
Triglycerides, high (mg/dL)			
Level 1 (>150)	201/309 (65.0)	214/300 (71.3)	-6.3 (-13.7, 1.1)
Level 2 (>300)	53/309 (17.2)	63/300 (21.0)	-3.8 (-10.1, 2.4)
Level 3 (>500)	14/309 (4.5)	13/300 (4.3)	0.2 (-3.1, 3.5)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is median 11.9 weeks (minimum 0.6, maximum 15.3 weeks).

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

None.

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

Not applicable.

23. Labeling: Key Changes and Considerations

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 148](#)). 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 148. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
BOXED WARNING	The Boxed Warning for embryo-fetal toxicity was revised for consistency with class labeling for this risk.
1 INDICATIONS AND USAGE	The Applicant's proposed indication was not substantively revised.
2 DOSAGE AND ADMINISTRATION	Revisions made in Dosage and Administration to reflect the decision (b) (4) Language regarding pregnancy testing prior to initiation, during therapy and after discontinuation was harmonized with the REMS.
4 CONTRAINDICATIONS	Contraindications revised to reflect class labeling for embryo-fetal risk.
5 WARNINGS AND PRECAUTIONS	The subsection for embryo-fetal risk was harmonized with class labeling; a subsection for the TRYVIO REMS was also added. The subsection for hepatotoxicity was revised to include additional description of the clinical trial experience and to include additional text for patients to report symptoms of hepatotoxicity. The subsections for fluid retention and hemoglobin decrease were revised to include additional descriptions of the clinical trial experience. A subsection for decreased sperm counts was added, consistent with class labeling.
6 ADVERSE REACTIONS	Details regarding (b) (4) were relocated to Section 5.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Language pertinent to Pregnancy, Lactation and Reproductive Potential were harmonized with class labeling. (b) (4) pertinent information was incorporated into (b) (4) Warnings and Precautions. In the Hepatic Impairment subsection, the proposed recommendation for patients with moderate hepatic impairment was revised to 'not recommended.'
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	The applicants proposed text for this subsection was not substantively revised.
12 CLINICAL PHARMACOLOGY	In the Mechanism of Action section, text thought not relevant or critical to describe the action of this product was removed. The Pharmacodynamics and Pharmacokinetic subsections were revised to be consistent with current Guidances.
13 NONCLINICAL TOXICOLOGY	Details regarding carcinogenicity studies were added. The 'Impairment of Fertility' section was revised to include additional data from studies with aprocitentan.
14 CLINICAL STUDIES	(b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	(b) (4) . In addition, the Applicant's table of results for the primary endpoint was updated to appropriately take into account assumptions for missing data. (b) (4) were removed and instead, a qualitative description of Part 3 describing the durability of the treatment effect on blood pressure was included.
17 PATIENT COUNSELING INFORMATION	The Patient Counseling section was revised to harmonize the pregnancy related language with class labeling, and to include text regarding the REMS.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	These sections were revised to reflect (b) (4)

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): N/A, not applicable; PI, prescribing Information

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide

24. Postmarketing Requirements and Commitments

The following postmarketing requirement will be required to assess a signal of a serious risk of embryo-fetal toxicity with the use of aprocitentan:

A worldwide descriptive study that collects prospective and retrospective data in women exposed to aprocitentan during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

25. Financial Disclosure

Table 149. Covered Clinical Study: PRECISION

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 248		
Number of investigators who are Sponsor 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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: not applicable Significant payments of other sorts: not applicable Proprietary interest in the product tested held by investigator: not applicable Significant equity interest held by investigator: not applicable Sponsor of covered study: not applicable		
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): 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

- Actelion Pharmaceuticals US, I, 2001, Prescribing Information: Tracleer (bosentan), accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209279s000lbl.pdf.
- Actelion Pharmaceuticals US, I, 2013, Prescribing Information: Opsumit (macitentan), accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204410s017lbl.pdf.
- Centers for Disease Control and Prevention, 2023, Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria From the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2017–2020, accessed, July 6, 2023, <https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html>.
- Daskalopoulou, SS, NA Khan, RR Quinn, M Ruzicka, DW McKay, DG Hackam, SW Rabkin, DM Rabi, RE Gilbert, RS Padwal, M Dawes, RM Touyz, TS Campbell, L Cloutier, S Grover, G Honos, RJ Herman, EL Schiffrin, P Bolli, T Wilson, RD Feldman, MP Lindsay, BR Hemmelgarn, MD Hill, M Gelfer, KD Burns, M Vallee, GV Prasad, M Lebel, D McLean, JM Arnold, GW Moe, JG Howlett, JM Boulanger, P Larochelle, LA Leiter, C Jones, RI Ogilvie, V Woo, J Kaczorowski, L Trudeau, SL Bacon, RJ Petrella, A Milot, JA Stone, D Drouin, M Lamarre-Cliche, M Godwin, G Tremblay, P Hamet, G Fodor, SG Carruthers, G Pylypchuk, E Burgess, R Lewanczuk, GK Dresser, B Penner, RA Hegele, PA McFarlane, M Sharma, NR Campbell, D Reid, L Poirier, SW Tobe, and P Canadian Hypertension Education, 2012, The 2012 Canadian hypertension education program recommendations for the management of hypertension: blood pressure measurement, diagnosis, assessment of risk, and therapy, *Can J Cardiol*, 28(3):270-287, <https://www.ncbi.nlm.nih.gov/pubmed/22595447>.
- Delyon, B, M Lavielle, and E Moulines, 1999, Convergence of a stochastic approximation version of the EM algorithm, *The Annals of Statistics*, 27(1):94-128, 135, <https://doi.org/10.1214/aos/1018031103>.
- Fukuroda, T, T Fujikawa, S Ozaki, K Ishikawa, M Yano, and M Nishikibe, 1994, Clearance of circulating endothelin-1 by ETB receptors in rats, *Biochem Biophys Res Commun*, 199(3):1461-1465, <https://www.ncbi.nlm.nih.gov/pubmed/8147891>.
- Gilead Sciences, I, 2007, Prescribing Information: Letairis (ambrisentan), accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022081s033lbl.pdf.
- Levey, AS, JP Bosch, JB Lewis, T Greene, N Rogers, and D Roth, 1999, A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group, *Ann Intern Med*, 130(6):461-470, <https://www.ncbi.nlm.nih.gov/pubmed/10075613>.
- Lixoft, 2021a, Monolix Documentation Version 2021, accessed November 1, 2022, <https://monolix.lixoft.com/>.
- Lixoft, 2021b, Simulx Documentation Version 2021, accessed November 1, 2022, <https://simulx.lixoft.com/>.

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Loffler, BM, V Breu, and M Clozel, 1993, Effect of different endothelin receptor antagonists and of the novel non-peptide antagonist Ro 46-2005 on endothelin levels in rat plasma, *FEBS Lett*, 333(1-2):108-110, <https://www.ncbi.nlm.nih.gov/pubmed/8224145>.

Marcoline, FV, J Furth, S Nayak, M Grabe, and RI Macey, 2022, Berkeley Madonna Version 10-A simulation package for solving mathematical models, *CPT Pharmacometrics Syst Pharmacol*, 11(3):290-301, <https://www.ncbi.nlm.nih.gov/pubmed/35064965>.

Ostchega, Y, CD Fryar, T Nwankwo, and DT Nguyen, 2020, Hypertension Prevalence Among Adults Aged 18 and Over: United States, 2017-2018, *NCHS Data Brief*, (364):1-8, <https://www.ncbi.nlm.nih.gov/pubmed/32487290>.

Persell, SD, 2011, Prevalence of resistant hypertension in the United States, 2003-2008, *Hypertension*, 57(6):1076-1080, <https://www.ncbi.nlm.nih.gov/pubmed/21502568>.

Pickering, TG, JE Hall, LJ Appel, BE Falkner, J Graves, MN Hill, DW Jones, T Kurtz, SG Sheps, and EJ Roccella, 2005, Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research, *Circulation*, 111(5):697-716, <https://www.ncbi.nlm.nih.gov/pubmed/15699287>.

FDA Draft Guidance for Industry: *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products* (September 2022), <https://www.fda.gov/media/90358/download>.

Wang, Y, PR Jadhav, M Lala, and JV Gobburu, 2012, Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies, *J Clin Pharmacol*, 52(10):1601-1606, <https://www.ncbi.nlm.nih.gov/pubmed/22162537>.

Whelton, PK, RM Carey, WS Aronow, DE Casey, Jr., KJ Collins, C Dennison Himmelfarb, SM DePalma, S Gidding, KA Jamerson, DW Jones, EJ MacLaughlin, P Muntner, B Ovbiagele, SC Smith, Jr., CC Spencer, RS Stafford, SJ Taler, RJ Thomas, KA Williams, Sr., JD Williamson, and JT Wright, Jr., 2018, 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, *Circulation*, 138(17):e426-e483, <https://www.ncbi.nlm.nih.gov/pubmed/30354655>.

27. Review Team

Table 150. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Sabry Soukehal
Nonclinical reviewer	Srinivasa Raju Datla
Nonclinical team leader	Jean Wu
OCP reviewer(s)	Brianna Cote, Hezhen Wang
OCP team leader(s)	Doanh Tran, Hao Zhu
Clinical reviewer	Selena DeConti
Clinical team leader	Rekha Kambhampati
Biometrics reviewer	Dali Zhou
Biometrics team leader	Jennifer Clark
Associate Director for Labeling	Michael Monteleone
Cross-disciplinary team leader and Deputy Division director (clinical)	Aliza Thompson
Deputy Division director (pharm/tox)	Calvin Lee Elmore
Division director (OCP)	Shirley Seo
Division director (OB)	Mark Rothmann
Office director (or designated signatory authority)	Lisa Yanoff

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

Table 151. Additional Reviewers of Application

Office or Discipline	Name(s)
OND/OCHEN/DCN	Norman Stockbridge, Mary Ross Southworth, Kirtida Mistry, Lori Wachter
OPQ	Akm Khairuzzaman, Ben Zhang, Zhengfu Wang, Ali Mohamadi, Liya Tang, Feiyan Jin, Rebecca Moody, Haritha Mandula, Grafton Adams
OPDP	Charuni Shah, Sapna Shah, Tierra Butler
OSI	Bei Yu, Tina Suyoung Chan
OND/DHN	George Makar, Paul Hayashi, Ling Lan, Edwige Chiogo Vouffo
OSE/DEPI	Marie Bradley, Margie Goulding, Mingfeng Zhang
OSE/DMEPA	Jody Kundreskas, Nicole Iverson
OSE/DPV	Courtney Suggs, Daniel Woronow
OSE/DRM	Cristen Lambert, Yasmeen Abou-Sayed, Laura Zendel, Monique Killen
OSE/OPE	Mark Avigan, Christian Cao
ORPURM/DPMH	Lynne Yao, Miriam Dinatale, Carrie Ceresa
IRT	Christine Garnett, Yanyan Ji, Michael Li, Dong Guo, Mario Sampson, Dalong Huang, Jing Sun
OMP/PLT	Laurie Buonaccorsi, LaShawn Griffiths

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; OND, Office of New Drugs; OCHEN, Office of Cardiology Hematology, Endocrinology and Nephrology; DCN, Division of Cardiology and Nephrology; OMP, Office of Medical Policy; PLT, Patient Labeling Team; OPE, Office of Pharmacovigilance and Epidemiology; ORPRUM, Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine; DPMH, Division of Pediatrics and Maternal Health; IRT, Interdisciplinary Review Team for Cardiac Safety Studies; DHN, Division of Hepatology and Nutrition; DPV, Division of Pharmacovigilance

27.1. Reviewer Signatures

Table 27-152 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Jennifer Clark OB DBII	Sections: 6.2, 16	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Jennifer Clark		Digitally signed by Jennifer Clark Date: 3/14/2024 4:18 PM EDT GUID: 2024314201816		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Sabry Soukehal ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Sabry Soukehal		Digitally signed by Sabry Soukehal Date: 3/14/2024 4:37 PM EDT GUID: 2024314203737		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Alexis Childers ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Alexis Childers		Digitally signed by Alexis Childers Date: 3/14/2024 4:46 PM EDT GUID: 2024314204625		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Rekha Kambhampati OCHEN DCN	Sections: 2.1, 2.2, 3, 4, 6.2.1.1, 6.2.1.2, 6.3, 10, 11, 15, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Rekha Kambhampati		Digitally signed by Rekha Kambham Date: 3/14/2024 4:47 PM EDT GUID: 2024314204739		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Michael Monteleone		Digitally signed by Michael Monteleone		
		Date: 3/14/2024 4:56 PM EDT GUID: 2024314205659		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Michael Monteleone		Digitally signed by Michael Monteleone		
		Date: 3/14/2024 4:57 PM EDT GUID: 2024314205730		

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Srinivasa Datla OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4 and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Srinivasa Datla		Digitally signed by Srinivasa Datla Date: 3/14/2024 9:46 PM EDT GUID: 202431514640		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Jean Wu OCHEN DPTCHEN	Sections: 5.1, 5.2 (pharmacology activity), 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jean Wu		Digitally signed by Jean Wu Date: 3/14/2024 10:06 PM EDT GUID: 2024315264		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.7, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore		Digitally signed by Calvin Elmore Date: 3/15/2024 8:36 AM EDT GUID: 202431512361		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Doanh Tran OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Doanh Tran		Digitally signed by Doanh Tran Date: 3/15/2024 8:37 AM EDT GUID: 202431512372		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Hao Zhu OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hao Zhu		Digitally signed by Hao Zhu Date: 3/15/2024 9:08 AM EDT GUID: 202431513825		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Division Signatory	Shirley Seo OCP DCEP	Sections: 5.2, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shirley Seo		Digitally signed by Shirley Seo Date: 3/15/2024 9:13 AM EDT GUID: 2024315131317		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Primary Reviewer	Cristen Lambert OMEPRM DRM	Sections: 7.7.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Cristen Lambert			Digitally signed by Cristen Lambert	
			Date: 3/15/2024 9:39 AM EDT GUID: 2024315133910	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Dali Zhou OB DBII	Sections: 6.2.1.3, 6.2.1.4, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dali Zhou			Digitally signed by Dali Zhou	
			Date: 3/15/2024 10:12 AM EDT GUID: 2024315141255	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Brianna Cote OCP DCEP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14.1, 14.2, 14.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Brianna Cote		Digitally signed by Brianna Cote Date: 3/15/2024 11:09 AM EDT GUID: 20243151599		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Secondary Reviewer	Yasmeen Abou-Sayed OMEPRM DRM	Sections: 7.7.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yasmeen Abou-Sayed		Digitally signed by Yasmeen Abou-S Date: 3/15/2024 11:46 AM EDT GUID: 2024315154649		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Mary Southworth OCHEN DCN	Sections: Safety	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Mary Southworth			Digitally signed by Mary Southworth Sign on behalf of Signing for Selena Date: 3/15/2024 12:16 PM EDT GUID: 2024315161627	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Risk Management Reviewer Discipline Tertiary Reviewer	Laura Zendel OMEPRM DRM	Sections: 7.7.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Laura Zendel			Digitally signed by Laura Zendel Date: 3/15/2024 2:45 PM EDT GUID: 2024315184556	

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 TRYVIO (aprocitentan)

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hezhen Wang OCP DPM	Sections: 14.5	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hezhen Wang		Digitally signed by Hezhen Wang Date: 3/16/2024 12:46 PM EDT GUID: 2024316164635		

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

/s/

ALIZA M THOMPSON
03/16/2024 04:21:50 PM

LISA B YANOFF
03/18/2024 06:04:58 AM