Multidisciplinary Review

Table 1. Application Information

Application type	NDA
Application number(s)	217202-Supplement 001
Priority or standard	Standard
Submit date(s)	12/19/2024
Received date(s)	12/19/2024
PDUFA goal date	10/19/2025
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	2/5/2026
Established/proper name	Landiolol hydrochloride
(Proposed) proprietary name	Rapiblyk
Pharmacologic class	Beta adrenergic blocker
Other product name(s)	
Applicant	AOP Health US, LLC
Dosage form(s)/formulation(s)	Intravenous infusion
Dosing regimen	In pediatric patients, start at 9 mcg/kg/min; adjust dose in 10-minute intervals as needed in increments of 9 mcg/kg/min to a maximum of 36 mcg/kg/min.
Applicant-proposed indication(s)/ population(s)	A beta-adrenergic blocker indicated for the short-term reduction of ventricular rate in adults (b) (4) with supraventricular tachycardia including atrial fibrillation and atrial flutter.
SNOMED CT code for proposed indication disease term(s)[1]	6456007, supraventricular tachycardia.
Regulatory action	Approval
Approved dosage (if applicable)	In pediatric patients, start at 9 mcg/kg/min; adjust dose in 10-minute intervals as needed in increments of 9 mcg/kg/min to a maximum of 36 mcg/kg/min.
Approved indication(s)/ population(s) (if applicable)	Rapiblyk is indicated for the short-term reduction of ventricular rate in: • adults with supraventricular tachycardia including atrial fibrillation and atrial flutter, and • pediatric patients with supraventricular tachycardia.
SNOMED CT code for approved indication disease term(s)[1]	6456007, supraventricular tachycardia.

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Landiolol is a beta adrenergic blocker initially approved by FDA on November 22, 2024, under 505(b)(2) pathway, as Rapiblyk indicated for the short-term reduction of ventricular rate in adults with supraventricular tachycardia including atrial fibrillation and atrial flutter. On December 19, 2024, the Applicant submitted NDA 217202/S-001 for Rapiblyk for the proposed indication of short-term reduction of ventricular rate in pediatric patients with supraventricular tachycardia (SVT). Evidence from adequate and well-controlled studies of landiolol in adults, coupled with pharmacokinetic, pharmacodynamic and safety data obtained from LANDI-PED study support the effectiveness and safety of landiolol in pediatric patients with SVT. Hence, an approval action is recommended for NDA 217202/S-001.

1.2. Basis of Regulatory Action

The LANDI-PED study was a prospective, multicenter, open-label, uncontrolled trial, designed to investigate the efficacy, safety, and pharmacokinetics (PK) of landiolol in pediatric patients. Sixty patients in surgical and non-surgical settings aged ≥1 day to <18 years with SVT of various etiologies (i.e., inappropriate sinus tachycardia, junctional ectopic tachycardia, focal atrial tachycardia, and atrio-ventricular re-entrant tachycardia) received landiolol as a continuous intravenous (IV) infusion starting with 5 µg/kg/min and titrated up to 40 µg/kg/min depending on the ventricular rate reduction for up to a maximum of 24 hours. The mean baseline ventricular rate (standard deviation) was 164 bpm (28 bpm).

The primary efficacy endpoint for LANDI-PED was percentage of patients with a heart rate (ventricular rate) reduction of at least 20% within 3.5 hours (210 min) (or earlier if infusion ended before 210 minutes) of the initiation of the landiolol infusion.

A total of 24 out of 60 (40%) subjects achieved the target heart rate reduction within the pre-specified time-period. The total number of subjects achieving the target ventricular rate reduction increased for longer infusion periods (i.e., 37 subjects for infusions up to 24 hours and 41 subjects for infusions up to 7 days). The mean (standard deviation) duration of treatment was 477 minutes (504 minutes).

Most of the patient population (95%) required dose escalation, with the vast majority (approximately 80%) titrated to the maximum dose of 40 µg/kg/min to achieve target heart rate reduction.

Key PK parameters in pediatric patients were similar to the adult data. Based on PK similarity between the pediatric and adult populations, dose-response relationship between landiolol and ventricular rate, established effectiveness of RAPIBLYK in the adult population, well understood

mechanism of action as a beta-1 blocker, and a favorable overall benefit-risk assessment, it is reasonable to conclude that the evidence provided under NDA 217202/S-001 is sufficient to support approval of landiolol for short-term reduction of ventricular rate in pediatric patients with supraventricular tachycardia.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	Supraventricular tachycardia (SVT): • Defined as a rapid heart rate originating from the atrial tissue above the atrioventricular (AV) node and interventricular septum. • SVT is a common condition in children. • Heart rates (HR) can range from 180 to 220 beats per minute (bpm). • Types of SVT include atrioventricular reentrant tachycardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT), atrial tachycardia, which includes atrial fibrillation, focal atrial tachycardia (FAT), multifocal atrial tachycardia and atrial flutter, and finally, junctional ectopic tachycardia (JET).	SVT is a common disease across all age groups in children.
Current treatment options	• AVRT, AVNRT: Intravenous adenosine is the first therapeutic option, and two doses are given in the setting of AVRT or AVNRT, according to the US Prescribing Information (USPI) for adenosine. If the arrhythmia is refractory or reinitiates after an initial response, the clinical strategy in inpatients is to use intravenous esmolol with escalation to amiodarone and procainamide for refractory SVT. These drugs, however, are not indicated for children. • JET: Initial treatment is supportive by decreasing sympathetic activation (e.g., sedation), minimizing inotrope/catecholamine use, normothermia or hypothermia. Amiodarone is used when these supportive measures do not resolve the arrythmia and propranolol or flecainide can be added. While beta-blockers will not convert the patient to	Adenosine is indicated for the conversion to sinus rhythm of paroxysmal SVT, including that associated with accessory bypass tracts. Several other anti-arrhythmic agents are used off-label for the treatment of SVT in pediatric patients.

	NSR, it can help reduce the heart rate allowing for atrial pacing and/or hemodynamic stability.	
Benefit	• Rapiblyk was administered by intravenous infusion at rates of 5, 10, 20 and 40 mcg/kg/min in children from birth to <18 years of age in Study LANDI-PED. This was a single arm, unblinded study whose primary endpoint was the percentage of subjects with ≥20% reduction in HR from baseline after 210 minutes of Rapiblyk infusion. • 60 subjects were enrolled with the following rhythms: inappropriate sinus tachycardia (IST), JET, AVRT, FAT, and a non-specified "other". • Among each of these groups there was at least one subject who had a ≥ 20% reduction in their HR from baseline.	Effectiveness of Rapiblyk for short-term control of ventricular rate has been established in adults through several randomized controlled trials. LANDI-PED study provides PK and pharmacodynamic data to support extrapolation of efficacy of Rapiblyk to pediatric patients with SVT. In LANDI-PED study, 24/60 (40%) subjects (including subjects with IST) met the primary endpoint of ≥20% reduction in heart rate (ventricular rate) from baseline, a dose-response relationship was observed for landiolol and ventricular rate, and the key PK parameters of Rapiblyk were similar to the adult population. These data provide evidence of effectiveness of Rapiblyk for short-term control of ventricular rate in pediatric patients with SVT.
Risk and risk management	• Safety was assessed in the 60 pediatric subjects with SVT or IST who received Rapiblyk. • The median duration of exposure was 210 minutes with a range of 20 to 1440 minutes; 37 (62%) had greater than 30 minutes of exposure and 22 (38%) had greater than 210 minutes of exposure. • 95% of subjects required dose escalation with approximately 80% requiring the maximum dose of 40 mcg/kg/min to achieve adequate heart rate control. • The most common adverse reaction was hypotension which occurred in 10% of the subjects. • Supportive safety data from adult patients showed a similar safety profile.	The key safety risk with Rapiblyk is hypotension. This risk can be clinically monitored and managed.

2.2. Conclusions Regarding Benefit-Risk

Rapiblyk was shown to decrease the ventricular rate in a dose-responsive and a duration-responsive manner in pediatric patients with SVT. The risk of Rapiblyk was consistent with the known risk of this drug class (i.e., hypotension). The review team assessed, and the CDTL agrees, that there were no new safety issues identified in the LANDI-PED trial. The benefit with Rapiblyk outweighs the risk, yielding a recommendation to approve Rapiblyk to include the pediatric population in the current label.

II. Interdisciplinary Assessment

3. Introduction

Disease Background

Supraventricular tachycardia (SVT) is defined as a rapid heart rate originating from the atrial tissue above the atrioventricular (AV) node and interventricular septum (Nizami et al. 2024). In SVT, heart rates can range from 180 to 220 beats per minute (bpm) (Patti et al. 2025). It is a common condition and affects 1 in 500 children (Borquez and Williams 2021). SVT can be caused by reentry circuits, abnormal automaticity, triggered activity, congenital heart disease, electrolyte imbalances and genetic predisposition. The resulting arrhythmias are atrioventricular reentrant tachycardia (AVRT), atrioventricular nodal reentrant tachycardia (AVNRT), atrial tachycardia, which includes atrial fibrillation, focal atrial tachycardia (FAT), multifocal atrial tachycardia and atrial flutter, and finally, junctional ectopic tachycardia (JET). JET can be congenital or occur as a sequela of cardiac surgery. Untreated and prolonged SVT can lead to hemodynamic compromise, tachycardia-induced cardiomyopathy and other complications.

In pediatric patients, the initial treatment for reentrant tachycardias is intravenous adenosine. If the arrhythmia is refractory to a second higher dose of adenosine, esmolol, dexmedetomidine, amiodarone, procainamide, or intravenous sotalol are used clinically (Batra et al. 2024). The management of JET involves sedation, minimizing the use of catecholamines and/or inotropes as these agents can activate the sympathetic nervous system and are arrhythmogenic and maintaining normothermia or inducing mild hypothermia. In children, amiodarone is the most commonly used anti-arrhythmic for JET and can be combined with propranolol or flecainide (Ashraf and Collier 2025).

Rapiblyk

In this sNDA, the Applicant is seeking approval for Rapiblyk, a beta-adrenergic receptor antagonist administered by intravenous infusion, for the treatment of children with SVT. According to the Applicant, Rapiblyk will reduce the ventricular rate in pediatric patients with SVT. The Applicant defines SVT to include IST, AVRT, AVNRT, FAT, atrial flutter, atrial fibrillation, and JET.

The pediatric study, LANDI-PED, was conducted in 10 centers in 4 European countries. The Applicant's rationale for assuming the applicability of foreign data to the population in the United States (US) was that the clinical rationale and approach to managing elevated heart rate due to SVT in pediatric patients are generally consistent between Europe and the US. Other than adenosine for AVRT and AVNRT, no antiarrhythmic agent is currently approved for the treatment of SVT in Europe or the US. Additionally, there is no evidence that there are significant genetic variations that would lead to differences in the metabolism of Rapiblyk between children in Europe and those in the US.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

The review team identified the following key review issues, discussed in detail under Section 6.3.

3.1.1.1. Does Rapiblyk Reduce Ventricular Rate in Pediatric Patients with SVT and IST?

3.1.2. Key Safety Review Issues

There were no key safety review issues identified.

3.2. Approach to the Clinical Review

The Applicant submitted efficacy and safety data from LANDI-PED, which was an open-label, single-arm phase 3 study evaluating the effectiveness and safety of Rapiblyk in controlling SVT and IST in pediatric patients. Efficacy was reviewed by Ann Punnoose, clinical reviewer and Ququan Liu, statistical reviewer, and safety was reviewed by Ann Punnoose, clinical reviewer. Dose-response was evaluated by Ande Anusha and Elly Moon, clinical pharmacology reviewers.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

RAPIBLYK is indicated for the short-term reduction of ventricular rate in:

- adults with supraventricular tachycardia including atrial fibrillation and atrial flutter, and
- pediatric patients with supraventricular tachycardia.

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR

   c. ✓ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]
3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

1 FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)*

[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

[3] FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)

Table 3. Clinical Trial Submitted in Support of Efficacy and Safety Determinations for Rapiblyk

Study Identifier	Study Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled	Number of Centers and Countries
LANDI-PED.	Pediatric patients aged ≥ 1 day up to 18 years who had undergone or were scheduled for cardiac or non-cardiac surgeries, and non-surgical patients who had sustained SVT lasting longer than 1 minute. Subjects with AVRT were enrolled only if they were refractory to adenosine, had relapsed after treatment with adenosine or had contra-indications to adenosine	Control type: none. Randomization: none. Blinding: none. Biomarkers: not applicable. Innovative design features: none.	Drug: Rapiblyk. Dosage: 5, 10, 20 and 40 mcg/kg/min. Number treated: 60. Duration (quantity and units): 24 hours.	Primary: Percentage of patients achieving heart rate reduction of at least 20% from baseline within 3.5 hours (210 min) of the initiation of Rapiblyk infusion.	60; 60.	10 Centers in 4 countries.

Source: Reviewer.

Abbreviations: HR, heart rate; h, hours, kg, kilograms; mcg, micrograms; min, minute; NSR, normal sinus rhythm; SVT, supraventricular tachycardia; wk, weeks

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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

Not Applicable.

5.2. Clinical Pharmacology/Pharmacokinetics

Not applicable.

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Applicant's Proposed Dosing Regimen for Pediatric Patients with Supraventricular Tachycardia

The proposed dosing regimen in pediatric patients is similar to that of approved adult dosing regimen with normal cardiac function.

Administer RAPIBLYK as a continuous intravenous infusion in a monitored setting, titrating as needed for heart rate control. There are limited data beyond 24 hours of use.

Start at 9 mcg/kg/min; adjust dose in 10-minute intervals as needed in increments of 9 mcg/kg/min to a maximum of 36 mcg/kg/min.

It should be noted that Rapiblyk (landiolol as free base) dose of 9 and 36 mcg/kg/min used in the Rapiblyk product labeling is equivalent to landiolol hydrochloride 10 and 40 mcg/kg/min, which was used throughout the review.

Selection of Dosing Regimen for Pediatric Study LANDI-PED

The LANDI-PED study was a multicenter, open-label phase 3 study designed to investigate the effectiveness, pharmacokinetics, pharmacodynamics, and safety of Rapiblyk in controlling supraventricular tachycardia in 60 pediatric patients stratified into two age groups: Group I (birth to less than 2 years, n=40) and Group II+III (2 to less than 18 years, n=20). The study assessed first-line treatment with LDLL300 in both surgical and non-surgical pediatric patients with various forms of supraventricular tachycardia including inappropriate sinus tachycardia, junctional ectopic tachycardia, atrial flutter, atrial fibrillation, and focal atrial tachycardia. Patients with atrioventricular reentrant tachycardia or atrioventricular nodal reentrant tachycardia were only treated if they were refractory to adenosine treatment.

The dose ranges to be used in the study depended on body weight and heart rate (HR) response of the patients. Following the initial dose of 5 mcg/kg/min, Rapiblyk was up titrated in order to achieve HR response or HR reduction above 20% if medically indicated and safe.

- Dose level 1: 5 mcg/kg/min
- Dose level 2: 10 mcg/kg/min
- Dose level 3: 20 mcg/kg/min
- Dose level 4: 40 mcg/kg/min

If the HR response was not achieved or HR reduction above 20% was medically indicated and safe at a specific dose level, after 10 min, the dose was increased (infusion rate was adapted) to the next

higher dose level. If at the time of any scheduled up-titration HR response was closely approached, the dose increase could, at the Investigator´s discretion, have been delayed up to 30 min of the specific dose level. If an increase in dosage was deemed unsafe by the Investigator, the current dose level could have been maintained. The treatment phase comprised of following phases:

- Infusion Phase I (V2): Treatment duration for Infusion Phase I (V2) was 30 minutes unless the patient had converted to normal sinus rhythm and no further Rapiblyk maintenance therapy was medically indicated or had experienced significant ADR.
- Infusion Phase II (V3): Treatment duration for Infusion Phase II (V3) was 180 minutes unless the patient had converted to normal sinus rhythm and no further Rapiblyk maintenance therapy was medically indicated or had experienced significant ADR.
- Prolongation Phase (V4): If after completion of Infusion Phase II (V3) a longer infusion duration was medically indicated and deemed safe and efficacious according to the Investigator, prolongation of infusion duration up to 24 hours (or until switch to oral therapy was possible) was allowed.
- Infusion End (V5): Time of Rapiblyk Infusion end. Rapiblyk infusion was terminated after 210 minutes or after 24 hours in case of infusion prolongation. This visit also applied to patients terminating the infusion earlier after achieving conversion to normal sinus rhythm or infusion termination for safety reasons.

The chosen dosages are within the range of doses used in previous clinical trials, which includes doses that have been reported for use of Rapiblyk in pediatric patients. There is limited experience with Rapiblyk infusion durations beyond 24 hours and doses higher than 40 mcg/kg/min. The initial starting dose in this study (5 mcg/kg/min) is half of the recommended starting dose for adults (10 mcg/kg/min), selected based on safety considerations for the pediatric population while maintaining the same maximum dose of 40 mcg/kg/min as used in adult studies. A maximum daily dose of 4032 mg has been defined for this study.

Assessment of the Proposed Dosing Regimen in Pediatric Subjects

The primary efficacy endpoint was achieved by 24/60 patients (40.0%) overall, with 14/40 patients (35.0%) in Group I and 10/20 patients (50.0%) in Group II+III achieving at least 20% heart rate reduction within 210 minutes. A clear dose-response relationship was demonstrated in both age groups, with response rates increasing from 5-15% at lower doses to 42.5-60% at the maximum dose of 40 mcg/kg/min. Although the starting dose of Rapiblyk was set at 5 mcg/kg/min (equivalent to 4.7 mcg/kg/min of landiolol as a free base), the applicant proposes a starting dose of 10 mcg/kg/min for pediatric patients, consistent with the adult dosing regimen. The clinical data clearly demonstrate that initiation of the treatment with such low initial dose is not necessary for safety purposes because Rapiblyk was well tolerated across all dose levels administered during the LANDI-PED study (up to 40 mcg/kg/min), and its overall safety profile in pediatric patients was consistent with that observed in adults. From an efficacy perspective, the study results indicate that a starting dose of 5 mcg/kg/min was largely sub-therapeutic. It is observed that 95% of patients required dose escalation, with the vast majority (approximately 80%) titrated to the maximum dose of 40 mcg/kg/min to achieve adequate heart rate control. Although a small number of patients exhibited > 20 % heart rate reduction at the starting dose of 5 mcg/kg/min, these effects were transient and not sustained over an extended period, necessitating further up-titration. Therefore, the review team determines that the proposed starting and maximum doses are acceptable.

Pharmacokinetics

A total of 16 patients were enrolled in the LANDI-PED PK sub-study, 11/40 (27.5%) patients in Group I and 5/20 (25.0%) patients in Group II + III. The pharmacokinetic (PK) and pharmacodynamic (PD) assessment supports the proposed starting dose and dose titration recommendations for the pediatric indication. Rapiblyk exposures in pediatric subjects in this study were consistent with exposures observed in adult patients. Key PK parameters demonstrated close alignment with adult data: elimination half-life (4.3 minutes median in pediatrics vs. 4.5 minutes in adults), total body clearance (46.0 mL/min/kg median in pediatrics vs. 57 mL/kg/min in adults following 20-hour continuous infusion of 37.3 mcg/kg/min), and volume of distribution (246.0 mL/kg median in pediatrics vs. 400 mL/kg in adults at steady state). The mean C_{max} values for Rapiblyk were 750.0 (±615.97), and 2168.2 (±1860.61) for Group I, and Group II + III, respectively. The C_{max} and AUC values differ by groups likely due to different doses received during dose titration and small sample size which led to high variability. However, the mean C_{max} values in pediatric patients are consistent with values of 699 and 1,990 ng/mL reported in a dose escalation study by Murakami et al. 2005. Descriptive statistics of PK parameters of landiolol are presented in Table 5 for the PK full analysis set (FAS) subset.

Table 5: Descriptive statistics of PK parameters of Rapiblyk (PK FAS subset)

PK parameter	Statistics	Group I N = 11	Group II + III N = 5	Overall N = 16
T_{max} [min]	Median (Range)	184 (33 - 1370)	1179 (32 – 1443)	210 (32 - 1443)
	n	10	5	15
C_{max} [ng/mL]	Mean (±SD)	750.0 (±615.97)	2168.2 (±1860.61)	1222.7 (±1308.4)
	n	10	5	15
AUC_{0-t} [min*ug/mL]	Mean (±SD)	429.51 (±457.82)	1455.66 (±1214.72)	771.56 (±898.35)
	n	10	5	15
$t_{1/2}$ [min]	Median (Range)	4.48 (3.26 – 5.34)	2.95 (1.74 – 8.2)	4.3 (1.74 – 802)
	n	8	5	13
Vdwa [mL/kg]	Median (Range)	486 (177 – 1209)	149 (53 – 204)	246 (53 – 1209)
	n	8	5	13

Source: Table 14.2.4.2.1.1 Clinical Study Report Ldll300301
Abbreviations: $AUC_{(0-t)}$, Area Under the Blood Concentration Curve from administration (0 h) to the last quantified concentration; C_{max}, Maximum Blood Concentration; min, minute; mL/kg, milliliter/kilogram; ng/mL, nanograms/milliliter; $t_{1/2}$, Half-life; Vdwa, Volume of Distr bution adjusted for body weight

Dose-Response Relationship

A clear dose-response relationship was demonstrated across both pediatric age groups, with progressive increase in heart rate response rates corresponding to escalating Rapiblyk doses. The highest therapeutic efficacy was consistently observed at the maximum dose of 40 mcg/kg/min in both age cohorts.

In Group I (birth to <2 years), the relative heart rate response rates demonstrated a stepwise increase from 5% at the initial 5 mcg/kg/min dose to 35.5% at the maximum 40 mcg/kg/min dose, with intermediate response rates of 2.6% and 11.4% at 10 and 20 mcg/kg/min, respectively. The

cumulative response analysis revealed progressive improvement, with 15% of patients achieving heart rate control by the 20 mcg/kg/min dose level and 42.5% by the maximum dose.

Group II+III (2 to <18 years) exhibited a similar dose-dependent pattern with enhanced overall responsiveness compared to the younger cohort. Relative heart rate response rates increased from 10% at 5 mcg/kg/min to 50% at 40 mcg/kg/min, with intermediate rates of 5.3% and 11.1% at 10 and 20 mcg/kg/min, respectively. Cumulative response rates showed 20% of patients achieving control by 20 mcg/kg/min and 60% by the maximum dose.

These findings support the proposed dose titration strategy and confirms that the maximum dose of 40 mcg/kg/min provides optimal therapeutic benefit across the pediatric age spectrum while maintaining an acceptable safety profile.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Study LANDI-PED

6.2.1.1. Design, Study LANDI-PED

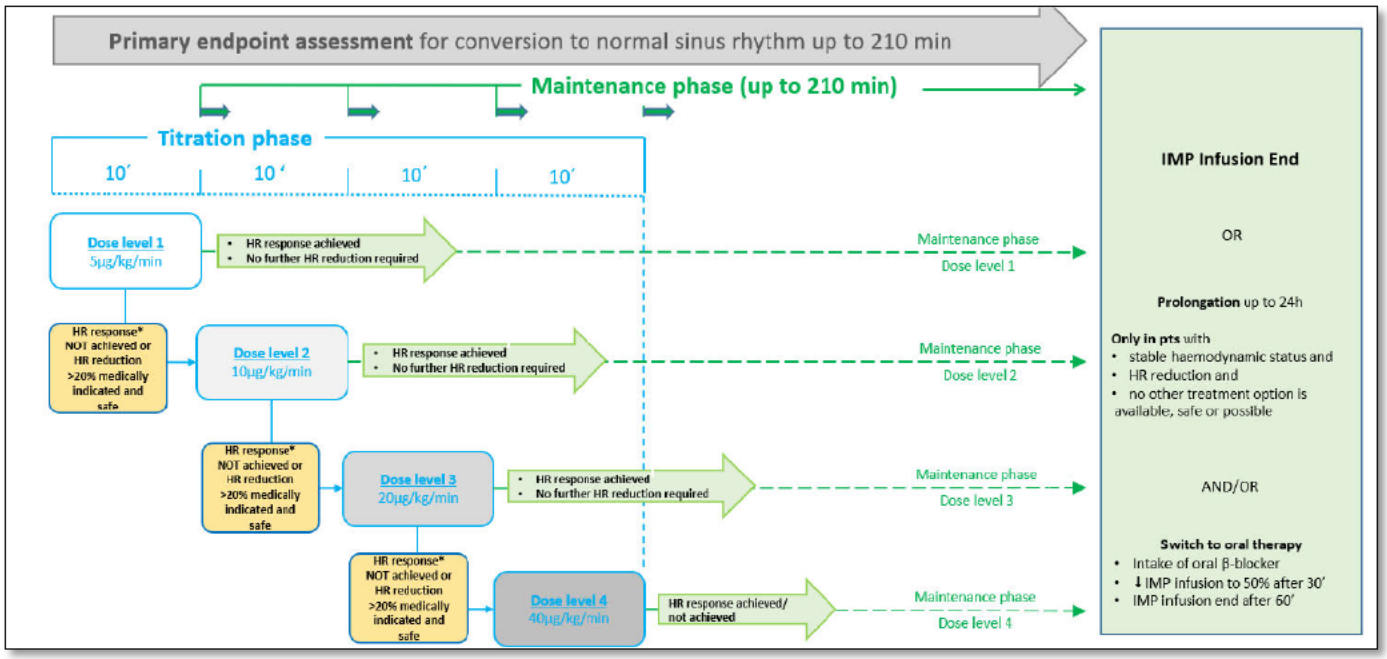
LANDI-PED was a phase 3, prospective, open-label single-arm study that enrolled 60 subjects with IST or SVT in 10 centers in 4 countries. The primary objective of this trial was to assess the PK and PD profile of Rapiblyk in the pediatric population. The secondary objectives included controlling SVT in the pediatric population, assessment of safety in the pediatric population, and the dose-response assessment for Rapiblyk in the pediatric population. Subjects were stratified by age into two groups:

- Group I: subjects from birth to < 2 years old
- Group II + III: subjects 2 to < 12 years old and 12 to < 18 years old.

Once subjects were diagnosed with IST or SVT, a Rapiblyk infusion was initiated. The doses were titrated as described in Section 6.1 with the goal of obtaining a “heart rate (HR) response”. The HR response, which was also the primary endpoint, was defined as achieving a ≥ 20% reduction from baseline HR. Thus, the effective dose of Rapiblyk was defined as the first dose at which a HR response was achieved.

If, after 10 minutes of treatment, a HR response was not achieved or if the clinical team determined that a HR reduction of more than 20% was necessary, the dose was increased to the next higher dose level up to a maximum of 40 mcg/kg/min. If the subject converted to a normal sinus rhythm (NSR) the effective dose could be maintained until 210 minutes and continued in the prolongation phase. The periods of treatment with Rapiblyk were divided into maintenance, prolongation (optional), infusion end, and follow-up phase, see Figure 1.

Figure 1. Trial Schematic, Study LANDI-PED



Source: LANDI-PED Clinical Study Report, NDA 217202, Figure 9.4-1

Rapiblyk Maintenance

Once subjects achieved the HR response, the effective dose would be maintained for 210 minutes unless a further up-titration (to a maximum dose of 40 mcg/kg/min) to obtain a HR response of > 20% was clinically indicated or if the subject experienced an adverse event (AE) requiring reduction or termination of the Rapiblyk infusion. If Rapiblyk was administered for 210 min, the highest possible dose was 40 mcg/kg/min for 180 min and the maximum dose was 7.55 mg/kg.

Rapiblyk Prolongation (optional)

According to the protocol, if the clinical team determined that the subject required Rapiblyk treatment for longer than 210 minutes, the Rapiblyk infusion could be prolonged for up to 24 hours or until the subject could be transitioned to oral therapy. A prolonged infusion duration was regarded as medically-indicated, safe and efficacious in subjects with stable hemodynamic response to Rapiblyk infusion and HR reduction, and when no other treatment option was available, safe or possible [e.g. no amiodarone therapy was indicated or possible, switch to oral alternative treatment (e.g. β-blocker) was not yet possible (e.g. due to sedation), cardiac pacing not (yet) possible/indicated or scheduled for a later time].

Rapiblyk Infusion End

According to the protocol, the duration of the Rapiblyk infusion was 210 min (3.5 hours) or latest after 24 hours (optional prolongation phase subjects only). The Rapiblyk infusion could have been terminated earlier than at 210 minutes for subjects who either converted to NSR and did not require further maintenance therapy or who experienced a significant AE that required infusion to be discontinued according to the investigator.

Follow-up Phase

After the Rapiblyk infusion ended, subjects were observed for an hour, and this was considered follow-up Visit I. Two additional follow-up visits were scheduled: one at 24h (follow-up Visit II) and a second at least 7 days (follow-up Visit III) after the end of the landiolol infusion.

6.2.1.2. Eligibility Criteria, Study LANDI-PED

Inclusion Criteria

- Informed Consent/assent from parents/legal representative(s) and children, if applicable.
- Children from birth to < 18 years
- Body weight ≥ 2.5 kg.
- Sustained supraventricular tachyarrhythmia for more than 1 minute.
- If a sub-type of paroxysmal supraventricular tachycardia (AVRT, AVNRT), refractory to treatment with adenosine, adenosine treatment relapsers and patients with contraindications to adenosine; or other forms of paroxysmal SVT not indicated for adenosine.

Exclusion Criteria

- Acute cardiogenic shock.
- Decompensated heart failure.
- Severe, uncorrectable metabolic acidosis.
- Ventricular tachycardia.
- Sick sinus syndrome (if there is no possibility for cardiac pacing) or clinically significant bradycardia.
- Acute asthma.
- Known pulmonary hypertension.
- Known stage 4 and 5 chronic renal disease.
- AV block 2nd or 3rd degree (if there is no possibility for cardiac pacing).
- Clinically significant hypotension.
- Postmenstrual age (gestational age + chronological age) <37 weeks.

- Untreated pheochromocytoma.
- End-stage disease.
- Pregnant or breast-feeding patients.
- Known hypersensitivity to any component of the study medication (e.g., Rapiblyk, mannitol).
- Participation in a clinical study or exposure to any study medication within 28 days before Rapiblyk infusion start, with the exception of Rapiblyk (end-of-study visit completed).

6.2.1.3. Statistical Analysis Plan, Study LANDI-PED

This description is based on the Statistical Analysis Plan (SAP), version 2, dated January 24, 2024. There was no statistical hypothesis testing. Because the study objectives were to assess PD/PK, and to assess safety, the results were analyzed only descriptively.

For categorical data, the standard set of summary statistics will be counts and percentages unless specified otherwise, i.e., unless 95% two-sided confidence intervals (CIs) for the percentages are also required as precision estimates.

For continuous data, the descriptive statistics presented will be: number of available observations, number of missing observations, mean, standard deviation (SD), median, lower quartile, upper quartile, minimum, and maximum. If needed, 95% two-sided CIs are presented as precision estimates.

For PK parameters, the descriptive statistics presented will be: number of available observations, number of missing observations, mean and geometric mean and their 95% CI, SD, SD of log-transformed data, median, minimum, and maximum.

Primary Endpoints:

The primary endpoint for LANDI-PED in the United States was the percentage of patients achieving a heart rate reduction of ≥ 20% from baseline within 3.5 hours (210) minutes of the initiation of the Rapiblyk infusion.

According to the finalized protocol (Version 7, May 2021), the primary endpoint was the percentage of patients who converted to normal sinus rhythm within 3.5 hours of the initiation of the Rapiblyk infusion. However, in a previous Type C meeting, dated July 14, 2020, the (then) Sponsor explained that they were revising the adult indication to focus on heart rate control in SVT and removing wording from their proposed labeling that suggested (b) (6) . This alternative primary endpoint was a change specific to the United States. The Sponsor proposed revising the pediatric study to specify heart rate control as the primary efficacy variable to be consistent with the revised adult indication. Because the NDA evaluating Rapiblyk for adults would be reviewed, the FDA agreed with revising the indication in adults, but the FDA recommended that the Sponsor submit a revised protocol and statistical analysis plan for LANDI-PED. However, these revised documents were not submitted for FDA review.

Secondary Endpoints:

The secondary endpoints were the following:

- Relative and cumulative improvement rates (at least 20% reduction from baseline HR) at each dosing level (before increase of treatment dose).
- Relative and cumulative non-response* rates at each dosing level.
- Percent change in HR from baseline at each time point.
- Relationship between change in heart rate from baseline and subject's age.
- Percentage of subjects converting to NSR (cardioversion) within 3.5 hours (210 min) of the commencement of the Rapiblyk infusion.
- Percentage of subjects showing sustained restoration of sinus rhythm for more than 24 hours and 1 week after Rapiblyk infusion end.
- Percentage of subjects for whom the infusion period was prolonged and duration of prolongation.
- Percentage of subjects achieving either NSR conversion or HR control at any time during the prolongation period.
- Time from start of Rapiblyk infusion until 20% reduction of HR is achieved.
- Time from start of Rapiblyk infusion until conversion to NSR is achieved.

6.2.1.4. Results of Analyses, Study LANDI-PED

This section presents subject disposition, baseline demographics, and results of the efficacy analyses for the primary and secondary efficacy endpoints.

Baseline Demographics

Patient demographic information is presented in Table 6. The mean age was 2.9 years, and the majority of the subjects were Caucasian. The median age was 0.69 months with a range of 5 days to 16 years.

Table 6. Baseline Demographics and Clinical Characteristics, Safety Population, Study Landi-Ped

Characteristic	Rapiblyk N=60
Sex, n (%)	
Male	26 (43%)
Female	34 (57%)
Age, years	
Mean (SD)	2.9 (4.3)
Median (min, max)	0.7 (5 days, 16)
Age group (years), n (%)	

≥0 to <1 month	6 (10%)
≥1 month to <1 year	29 (48.3%)
≥1 year to < 6 years	16 (26.7%)
≥6 years to <12 years	4 (6.7%)
≥ 12 years to <18 years	5 (8.3%)
Group	
Group I (0 to <2 years)	40 (66.7%)
Group II (≥ 2 years to < 12 years) + Group III (≥12 years to <18years)	20 (33.3%)
Race, n (%)	
Asian	1 (1.7%)
Black or African American	1 (1.7%)
White	54 (90%)
Other	4 (6.7%)
Country of participation, n (%)	
Austria	19 (31.7%)
German	36 (60%)
Hungary	4 (6.7%)
Spain	1 (1.7%)
Surgical Status, n (%)	
Non-surgical	17 (28.3%)
Perioperative	14 (23.3%)
Postoperative	29 (48.3%)
Baseline arrhythmia, n (%)	
IST	30 (50%)
JET	12 (20%)
FAT	8 (13.3%)
AVRT	7 (11.7%)
Other	3 (5%)

Source: Reviewer based on adsl.xpt dataset
Abbreviations: AVRT, atrioventricular reentrant tachycardia; FAT, focal atrial tachycardia; IST, inappropriate sinus tachycardia; JET, junctional ectopic tachycardia; N, number of patients in treatment arm; n, number of patients with given characteristic; SD, standard deviation

Patient Disposition

Disposition information is presented in Table 7. A total of 60 subjects were enrolled in the study. While 37 subjects discontinued the study drug, this was due to conversion to NSR in 15 subjects. Only 1 subject discontinued the study drug within the first 30 minutes, 16 subjects discontinued between 30 minutes and 210 minutes, and 21 subjects discontinued 210 minutes after the Rapiblyk infusion was initiated.

Table 7. Patient Disposition, Study LANDI-PED

Parameter	Rapiblyk N=60 n (%)
Subjects enrolled	60
Full analysis set	60 (100%)
Per protocol population	55 (91.7%)
PK analysis set	28 (46.7%)
Discontinued study drug	37 (61.7%)

Conversion to NSR	15 (25%)
Lack of efficacy	15 (25%)
Safety reasons	7 (11.7%)
Discontinued study	2 (3.3%)
Lost to follow-up	1 (1.7%)
Other[1]	1 (1.7%)

Source: Table 10.1-1 from the CSR
[1]Transferred to another hospital
Abbreviations: NSR, normal sinus rhythm; PK, pharmacokinetic

6.3. Key Efficacy Review Issues

6.3.1. Does Rapiblyk Reduce Ventricular Rate in Pediatric Patients with SVT and IST

Issue

Whether the open-label single-arm study (LANDI-PED) shows that Rapiblyk reduces ventricular rate in pediatric patients with SVT and IST.

Background

Among the 60 subjects enrolled in LANDI-PED, several arrhythmias were represented (Table 9). These included atrioventricular reentrant tachycardia (AVRT, n = 7), junctional ectopic tachycardia (JET, n =12), and focal atrial tachycardia (FAT, n = 8). There were 3 subjects whose arrhythmias were not specified and 30 subjects with inappropriate sinus tachycardia (IST). According to the Applicant, site investigators could enroll patients with IST if they decided these patients would benefit from HR reduction. There was no HR threshold required for enrollment and the site investigators did not have to identify the parameter (hemodynamic measurement, indicator of appropriate cardiac output) they intended to improve by lowering the heart rate.

The primary endpoint of LANDI-PED, in the United States, was the percentage of subjects achieving a heart rate reduction of ≥ 20% from baseline within 3.5 hours (210) minutes of the initiation of the Rapiblyk infusion. Of note, this does not require that the arrhythmia be resolved, and that the subjects' rhythms revert to NSR. Indeed, treatment with a beta-blocker in arrhythmias such as JET will not likely lead to resolution of the arrhythmia. Instead, a decrease in heart rate could lead to hemodynamic improvement or allow atrial or atrioventricular (AV) sequential pacing, thereby improving cardiac output (Sasikumar et al 2021).

Assessment

There were several limitations in the LANDI-PED's design. For instance, LANDI-PED was an open-label study with no control group. Therefore, the proportion of subjects with a 20% decrease from baseline heart rate could not be compared to the proportion of such a decrease with the currently used standard of care or other therapies used to treat SVT.

Additionally, 50% of the subjects enrolled in the study had IST (n = 30). The Applicant did not use a consistent definition of IST for all subjects participating in the study and the reasons for initiating Rapiblyk in these subjects were not specified in the protocol or recorded in the Clinical

Study Report. In the United States, the treatment of sinus tachycardia requires identifying the underlying etiology and the elevated heart rate by itself is not considered a reason to treat. IST is a chronic condition that is not associated with physiologic, pharmacologic, or pathologic etiology (Henning and Krawiec 2023).

In total, 24 of the 60 (40%) subjects met the primary endpoint with a reduction of ≥ 20% in their heart rate compared to baseline (Table 9).

Table 8 below shows the subjects classified by baseline arrhythmia, and the percentage change from baseline HR at 30-minute intervals since Rapiblyk initiation until 210 minutes when the infusion ended. Subjects with IST and the other SVTs experienced a decrease in HR from baseline, however, it was only subjects with AVRT who, on average, met the primary endpoint in that they had a >20% decrease in heart rate from baseline at 120, 150, 180 and 210 minutes after initiation of the Rapiblyk infusion.

Table 8. Percentage of change from baseline in heart rate by time point and arrythmia type at baseline

			Percentage change from baseline in HR [%]						
SVT type at baseline	Number of subjects at baseline	Average duration of infusion [min]	30 min	60 min	90 min	120 min	150 min	180 min	210* min
IST	30	507.0	n = 29 -5.44	n = 29 -9.00	n = 27 -7.74	n = 28 -10.20	n = 28 -9.44	n = 26 -12.20	n = 25 -12.37
JET	12	317.8	n = 12 -2.73	n = 11 -3.19	n = 10 -7.10	n = 8 -1.27	n = 7 -6.70	n = 7 -2.73	n = 7 -6.66
FAT	8	369.9	n = 7 -8.96	n = 7 -11.58	n = 8 -15.25	n = 8 -14.12	n = 8 -13.22	n = 7 -15.14	n = 7 -14.80
AVRT	7	694.0	n = 7 -6.71	n = 6 -17.04	n = 6 -17.27	n = 5 -27.26	n = 5 -32.61	n = 5 -28.12	n = 4 -28.51
Other	3	591.7	n = 3 -5.66	n = 3 -7.32	n = 3 -2.91	n = 3 -14.69	n = 3 -8.59	n = 2 -9.72	n = 2 -10.97

n = total number of patients with available data at specified timepoint.
*If scheduled 210 min timepoint is not performed, then Infusion End performed at 210 min or Unscheduled Infusion Phase II timepoints performed around 210 min are taken into consideration.
Source: Table 4 (Appendix 1: Additional results – POST-CSR 4)

Table 9 below shows that at least 1 subject with IST and every type of SVT met the primary endpoint, experience a ≥ 20% reduction in HR from baseline after treatment with landiolol.

Table 9. Subjects with ≥ 20% reduction in HR compared to baseline by arrhythmia type at baseline

Arrhythmia at baseline	Number of subjects	Subjects with the ≥20% reduction in HR from baseline (%)	95% CI for proportion
IST	30	10 (33.3)	16.56; 50.2
JET	12	3 (25)	0.5; 49.5
FAT	8	4 (50)	15.4; 84.6
AVRT	7	6 (85.7)	59.8; 100
Other	3	1 (33.3)	0; 86.7

Source: Table 11.4-21 Percentage of patients with the primary response by SVT type at baseline (FAS) from the CSR

Abbreviations: AVRT, atrioventricular reentrant tachycardia; CI, confidence interval; FAT, focal atrial tachycardia, HR, heart rate; IST, inappropriate sinus tachycardia; JET, junctional ectopic tachycardia

Table 10 below shows the number of subjects by rhythm type who responded to the different doses of landiolol that were administered in LANDI-PED. In each rhythm, the highest responder rate was seen when subjects received 40 mcg/kg/min. See Section 6.1:Assessment of Dose and Potential Effectiveness.

Table 10: Dose-response relationship by rhythm-type

Rhythm	Dose (mcg/kg/min)	N (total) who received this dose	# of subjects who had ≥ 20% reduction in HR from baseline	% Responder Rate
IST	5	30	2	6.7
	10	28	2	7.1
	20	26	2	7.7
	40	24	10	41.6
JET	5	12	0	0
	10	12	0	0
	20	10	1	10
	40	9	2	22.2
FAT	5	8	2	25
	10	7	0	0
	20	7	1	14.3
	40	7	2	28.6
AVRT	5	7	0	0
	10	7	0	0
	20	7	2	28.5
	40	6	5	83.3
Other	5	3	0	0
	10	3	0	0
	20	3	0	0
	40	3	1	33.3

Source: Reviewer
Abbreviations: AVRT, atrioventricular reentrant tachycardia; FAT, focal atrial tachycardia, HR, heart rate; IST, inappropriate sinus tachycardia; JET, junctional ectopic tachycardia

Conclusion

Rapiblyk decreased the ventricular rate by ≥ 20% in pediatric subjects with IST and different types of SVT. Additionally, a dose-response relationship was observed for Rapiblyk and decrease in ventricular rate, with a highest response rate seen at the highest dose of Rapiblyk administered, or 40 mcg/kg/min.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Not applicable as no new nonclinical pharmacology/toxicology data were submitted in this efficacy supplement.

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

Rapiblyk is a beta-adrenergic receptor antagonist, and the potential serious risks listed in the class labeling include bradycardia, hypotension, hypoglycemia, worsening heart failure, bronchospasm, hyperkalemia, and hypersensitivity. Other commonly reported adverse reactions listed in the labeling for beta blockers approved for use in pediatrics include sleep disturbance, agitation, peripheral coldness, fatigue, dizziness and diarrhea.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

Rapiblyk was approved in adults on November 22, 2024, and according to the most recent periodic adverse drug experience report (PADER; submitted June 18, 2025) the product is not yet marketed in the US.

7.4. FDA Approach to the Safety Review

Safety data from LANDI-PEDs was submitted to support the safety of Rapiblyk. The safety population consists of 60 patients who received at least one dose of Rapiblyk. These subjects' ages ranged from 5 days to 16 years. Of the 60 subjects, 17 were non-surgical patients, 14 were perioperative and 29 were postoperative.

The frequencies of each adverse event (AE) were assessed and described by occurrence. The review team reviewed all adverse events of special interest (AESI), serious adverse events (SAEs), discontinuations, withdrawals and patients lost to follow up.

Additionally, the Applicant is relying on safety information from the original NDA in which Rapiblyk was approved for adults (November 2024).

7.5. Adequacy of the Clinical Safety Database

The safety database along with the safety information from the original NDA was adequate for a sufficient safety assessment Rapiblyk for the indication of decreasing ventricular rate in pediatric patients with SVT and IST. The review team did not identify any major data quality of integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to the coding of adverse events.

Table 11 summarizes the Rapiblyk exposure for the safety population. Subjects treated for ≥180 min to ≤210 min (41.7%) comprise the largest cohort. The second largest cohort were those treated for >210 min to <24h (36.7%).

Table 11. Duration of Exposure, Safety Population, Studies LANDI-PED

Parameter	Rapiblyk N=60
Duration of treatment (minutes)	
Mean (SD)	476.9 (504)
Median (min, max)	210 (20, 1440)
Patients treated, by duration, n (%)	
Any duration (at least one dose)	
0 to <30 min	1 (1.7%)
≥30 min to <60 min	2 (3.3%)
≥60 min to <90 min	2 (3.3%)
≥90 min to <120 min	2 (3.3%)
≥120 min to <150 min	3 (5%)
≥150 min to <180 min	3 (5%)
≥180 min to ≤210 min	25 (41.7%)
>210 min to <24h	22 (36.7%)

Source: Reviewer
Abbreviations: min, minutes; N, number of patients in treatment arm; n, number of patients with given treatment duration; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Study LANDI-PED

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study LANDI-PED

As Table 12 shows, one or more treatment emergent adverse events (TEAE) was reported by 35 (58.3%) of the subjects treated with Rapiblyk. The majority of the events were categorized as moderate or severe.

Table 12. Overview of Adverse Events, Safety population, Study LANDI-PED

Event Category	Rapiblyk N = 60 n (%)
Subjects with any AE	35 (58.3)
Number of AE	49
Moderate or severe AEs	29 (59.2)
Any SAE	6 (12.2)
SAE with fatal outcome	1 (2)
AE leading to discontinuation of study drug	8 (16.3)
AE leading to dose modification of study drug	1 (2)
AE leading to interruption of study drug	0
AE leading to reduction of study drug	1 (2)

Source: adae.xpt, reviewer
Abbreviations: AE, adverse event, N, number of subjects in treatment arm; n, number of subjects or events; SAE, serious adverse event

7.6.1.2. Deaths, Study LANDI-PED

During LANDI-PED, one subject who received Rapiblyk died.

- LDLL300.301-(b) (6): This was an 8-month-old female infant who underwent commissurotomy of the pulmonary valve, patch enlargement of the pulmonary artery root, the trunk and the two pulmonary artery branches, on (b) (6). She was diagnosed with IST on (b) (6), and a Rapiblyk infusion was started at 5 mcg/kg/min. According to the narrative, approximately 24 hours later, the Rapiblyk infusion was terminated due to "achievement of timepoint 210 minutes (or later) with sufficient clinical improvement". On (b) (6), 2 weeks after having finished the Rapiblyk infusion, the subject experienced right ventricular failure and died. The Applicant assessed this death as being unrelated to Rapiblyk; the review team agreed with this assessment.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Study Landi-PED

Table 13 lists the 6 SAEs reported in 4 subjects. One subject, a 7-year-old male experienced hypotension within 15 minutes of being administered Rapiblyk at 40 mcg/kg/min. The Applicant did not report the exact blood pressure, but noted that the subject developed nausea, vomiting, sweating, shivering and dizziness. The infusion was discontinued and replaced with esmolol. The subject's hypotension resolved. The Applicant concluded that this was related to Rapiblyk and the review team agreed.

The Applicant assessed the other SAEs as unrelated to Rapiblyk and the review team agreed with the Applicant's assessments.

Table 13. Serious Adverse Events[1], LANDI-PED

Preferred Term	Rapiblyk n = 60
Any SAE	6
Hypotension	1
Cardiac Tamponade	1
Pulmonary hypoperfusion[2]	1
Right ventricular failure[2]	2
Toxicity to various agents	1

Source: ADAE.xpt
[1] 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.
[2] One subject had both pulmonary hypoperfusion and right ventricular failure.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SAE, serious adverse event

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Study LANDI-PED

Thirty-seven (61.7%) subjects discontinued Rapiblyk during the study and 7 subjects out of the 37 discontinued Rapiblyk due to safety reasons.

As shown in Table 14, the TEAEs in 5 of the subjects who discontinued Rapiblyk due to TEAEs were assessed by the review team as being related to Rapiblyk, one was unrelated to Rapiblyk and in one, the relationship to Rapiblyk could not be determined.

Table 14. Adverse Events Leading to Discontinuation by Subject, LANDI-PED

Patient ID Number	AE Leading to Study Discontinuation	Relationship to Drug[1]
LDLL300.301-(b) (4)	Hypotension	Related
LDLL300.301-	Hypotension	Related
LDLL300.301-	Hypotension	Related
LDLL300.301-	Hypotension	Related
LDLL300.301-	Hypotension	Related
LDLL300.301-	EKG abnormality: prolonged QRS duration	Unrelated
LDLL300.301-	Hypotension	Unable to assess

Source: ADSL.xpt
[1] Review Team assessment
[2] According to the Applicant's narrative, this subject discontinued due to hypotension that was due to the refractory underlying arrhythmia (JET), but the subject was receiving landiolol at 40 mcg/kg/min at the time of hypotension.
Abbreviations: EKG, electrocardiogram; JET, junctional ectopic tachycardia; PT, preferred term

7.6.1.5. Treatment-Emergent Adverse Events, Study LANDI-PED

The frequency and severity of TEAEs were evaluated to assess the general safety profile of Rapiblyk. TEAEs are AEs that developed, worsened or became serious during the treatment period. This assessment of safety is in addition to the safety assessment performed during the approval of the original NDA for the use of Rapiblyk in adults in November 2024.

The review team assessed frequent AEs to be adverse reactions (ARs) if they could be explained by Rapiblyk drug class (beta-blocker) or its mechanism of action. Table 15 shows TEAEs that occurred in ≥2% of all subjects who received Rapiblyk in LANDI-PED. Only 1 subject required a reduction in the dose of Rapiblyk and 8 required discontinuations of the infusion.

Hypotension is a known AR of this drug class and of the mechanism of action of beta blockers. While the other AEs occurred more than once, they are more likely to be related to the subjects' primary illness rather than their exposure to Rapiblyk.

Table 15. Adverse Events, LANDI-PED

Preferred Term	Rapiblyk (N = 60)
Any AE	49
Hypotension	8
Pleural effusion	5
Sinus tachycardia	5
Infection	3
Supraventricular tachycardia	3
Hypokalemia	2
Right ventricular failure	2

Source: ADAE.xpt
Abbreviations: AE, adverse event; N, number of patients in treatment arm; PT, preferred term

7.6.1.6. Laboratory Findings, Study LANDI-PED

Overall Summary

Routine safety monitoring blood work (hematology, clinical chemistry), and creatinine kinase, and troponin, were obtained throughout LANDI-PED.

Hematological analyses

The review team focused on the following hematological bloodwork obtained during this study: white blood cell count, hemoglobin, hematocrit, and platelets. In most cases, baseline date for these components of the complete blood cell count were available for the 60 subjects. Results for most of the components were normal throughout the study.

Kidney Function

Kidney function remained normal throughout the study in most of the subjects

Electrolyte Trends

Sodium, potassium, chloride, calcium, and blood glucose were followed throughout the study. While several subjects had abnormally high and low results, on the review team's assessment, these results were not clinically significant, or they normalized with the follow-up assessment.

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study LANDI-PED

Of the 60 subjects in LANDI-PED, only 42 had the liver function tests required to assess for drug induced liver injury (DILI). As shown in Table 16 below, there were: no Hy's Law cases, 4 Temple's Corollary cases, and 3 cholestasis cases.

Table 16: Potential DILI, LANDI-PED

Quadrant	Rapiblyk (n = 42)*
Potential Hy's Law (right upper)	0
Cholestasis (left upper)	3 (7.1%)
Temple's Corollary (right lower)	4 (9.5%)
Total	7 (16.7%)

Source: adlb.xpt, Reviewer
*Only 42 subjects had the laboratory data required for DILI analysis, which is at least one post-baseline value for ALP, AST, ALT, and bilirubin. Percentages of subjects meeting the criteria are, therefore, out of 42.
Abbreviations: DILI, drug-induced liver injury; N, number subjects

On evaluation of these 7 subjects and their bloodwork, the liver function abnormalities could not be clearly attributed to their exposure to Rapiblyk. Based on the mechanism of action of Rapiblyk, a beta blocker, it is unlikely that Rapiblyk caused hepatotoxicity. No additional hepatic monitoring is recommended in patients who are treated with Rapiblyk.

7.6.1.8. Vital-Sign Analyses, Study LANDI-PED

The review team's vital sign analyses focused on heart rates, and systolic and diastolic blood pressures. See Section 6.3 for a discussion of heart rates and Sections 7.6.1.4 and 7.6.1.5 for a discussion of blood pressure.

7.6.1.9. Subgroup Analyses

Not applicable.

7.6.1.10. Exposure-Adjusted Analyses

Not applicable.

7.7. Key Safety Review Issues

No key safety issues were identified.

8. Therapeutic Individualization

The same intrinsic and extrinsic factor considerations that apply to adults are applicable to the pediatric population.

8.1. Intrinsic Factors

Renal Impairment:

No dose adjustment is necessary in pediatric patients with renal impairment. There is no dose adjustment in adult patients with any degree of renal impairment. Although the effect of renal impairment on landiolol pharmacokinetics has not been specifically studied in adult patients, renal excretion represents less than 10% of landiolol elimination, with the primary elimination pathway being metabolism by pseudocholinesterases and carboxylesterases. Given the short-term nature of landiolol therapy (typically up to 24 hours) and the minimal contribution of renal elimination to overall drug clearance, dose modifications based on renal function are not warranted in the adult and pediatric population.

Hepatic Impairment:

No dose adjustment is recommended for pediatric patients with mild hepatic impairment (Child-Pugh Class A). Adult data demonstrate that mild hepatic impairment results in a 44% increase in AUC and 42% increase in Cmax compared to subjects with normal hepatic function. However, given the wide therapeutic dose range of landiolol (5-40 μg/kg/min) and the ability to titrate doses based on individual patient response, this magnitude of exposure increase can be accommodated within the established dosing framework. The use of landiolol should be avoided in patients with moderate and severe hepatic impairment (Child-Pugh Class B or C) because their effect on landiolol pharmacokinetics in patients has not been characterized. The approved label indicates – "Avoid use of Rapiblyk in patients with moderate or severe hepatic impairment (Child-Pugh B or C)."

8.2. Extrinsic Factors

Drug Interactions:

No dose adjustments are necessary in pediatric patients receiving concomitant medications that are substrates of major cytochrome P450 enzymes. Landiolol is primarily metabolized by pseudocholinesterases and carboxylesterases rather than CYP enzymes, minimizing the potential for clinically significant drug-drug interactions. Based on in vitro data reviewed in the original submission, landiolol and the metabolite M1 do not cause any clinically relevant drug interactions mediated through CYP enzymes.

8.3. Plans for Pediatric Drug Development

When Rapiblyk was approved for adults in November 2024, the following post-marketing

requirement (PMR) for the pediatric drug development of Rapiblyk was issued:

PMR # 7410-2: Multicenter, Open-label Study to Investigate the Effectiveness and Safety of AOP Landiolol in Controlling Supraventricular Tachycardia in Pediatric Patients (LANDI-PED)

An Agreed initial pediatric study plan (iPSP) was issued on November 16, 2017. The pediatric study requirement for the indication of SVT in children from birth to <18 years of age was deferred until December 2024 because the product was ready for approval for use in adults and pediatric study had not yet been submitted. At a type C meeting, dated July 14, 2020, the FDA suggested that the (then) Sponsor consider submitting a proposed pediatric study request (PPSR) for a Written Request based on LANDI-PED because there are no beta-blocker drug products approved in the US for ventricular rate control in pediatric patients. The Sponsor submitted a PPSR in January 2024. However, the FDA declined to issue a Written Request because the design of the proposed pediatric study was uncontrolled such that the primary endpoint would be difficult to interpret. The FDA recommended that the Sponsor resubmit a proposed pediatric study with a trial that is randomized and placebo-controlled in design.

In their iPSP submitted October 2017, the Sponsor presented their justification for their open-label single arm study, which was as follows:

1. The inclusion of a placebo-arm in post-operative SVT would be considered unethical.
2. The inclusion of an active control arm would be infeasible because while several antiarrhythmic drugs are used off-label for the treatment of SVTs, none are approved for acute rate control in the pediatric population. The Sponsor did not consider it ethical to compare Rapiblyk to another antiarrhythmic that is also currently not approved for rate control in children within the same clinical trial.

The following PMR schedule milestone was agreed upon with the Applicant:

Final Report Submission: 12/31/2024

This supplemental NDA was presented at the Pediatric Review Committee (PeRC) on October 7, 2025. The PeRC and the review team agreed that Rapiblyk was assessed for patients aged 0 to 17 years and that the PREA PMR has been fulfilled.

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

Not applicable.

9. Product Quality

Not applicable. No new information pertaining to product quality was submitted.

Quality microbiology review team: This supplement proposes to expand the indication to include pediatric population. Because the weight of pediatric population is lower than that of adults, quality microbiology review team performed calculation to make sure that the worst-case endotoxins exposure is within USP<85> for this population. These calculations showed that the

endotoxins exposure for the pediatric population meets USP<85> recommendation.

9.1. Device or Combination Product Considerations

Not applicable.

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

Human Subjects Protections

As stated by the Applicant, the clinical trials were conducted in substantial conformance with International Council for Harmonization good clinical practice requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. All studies submitted in this application were conducted according to FDA requirements, under investigational new drug (IND) 131338.

Clinical Site Inspections

Clinical site inspections were not performed.

Financial Disclosures

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance Financial Disclosure by Clinical Investigators (February 2013) (see Section 25), and by 21 CFR 54.4. None of the investigators of the study were employed by the Applicant, and none disclosed financial interests with the Applicant. In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application. It did not raise challenging efficacy or safety issues that needed external input.

III. Additional Analyses and Information

12. Summary of Regulatory History

AOP Orphan Pharmaceuticals submitted NDA 217202 using the 505(b)(2) pathway by relying on

published data from the landiolol hydrochloride product approved outside the USA (Onoact) on May 31, 2022. Landiolol hydrochloride was approved in the European Union (EU) as Rapibloc and in Japan as Onoact.

The Applicant developed Rapiblyk 300 mg, a sterile lyophilized powder, which is approved in the EU. The Applicant performed additional non-clinical studies addressing receptor binding, including ion channels, for parent and major human metabolites. Studies to qualify the impurities are ongoing. The Applicant also completed 3 pharmacokinetic (PK)/pharmacodynamic (PD) studies in healthy Caucasian subjects and one PK/PD study in Caucasian subjects with tachycardic atrial fibrillation (AF) or atrial flutter (AFl).

Rapiblyk was approved on November 22, 2024, wherein there was a postmarketing requirement, PMR 7410-2 – Study LDLL300.301: Multicenter, Open-label Study to Investigate the Effectiveness and Safety of AOP Rapiblyk in Controlling Supraventricular Tachycardia in Pediatric Patients (LANDI-PED), to submit a pediatric study report for the study by December 31, 2024. This supplemental application includes the final study report for PMR 7410-2 – Study LDLL300.301: Multicenter, Open-label Study to Investigate the Effectiveness and Safety of AOP Rapiblyk in Controlling Supraventricular Tachycardia in Pediatric Patients (LANDI-PED) and revised labeling.

The Supplement was discussed on September 1, 2025, 505(b)(2) clearance meeting and it is cleared for action from a 505(b)(2) perspective.

AOP Orphan Pharmaceuticals GmbH submitted the notification of change of the ownership to AOP Health US LLC on October 13, 2025.

13. Pharmacology Toxicology

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

Not applicable.

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

Not Applicable

14. Clinical Pharmacology

14.1. Bioanalytical Method Validation and Performance

Landiolol and its metabolites in precipitated human whole blood were determined by a validated high-performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) method

developed at [redacted] (b) (6). The samples were prepared via protein precipitation. Detection was done by tandem mass spectrometry (API 6500 II) in the multiple reaction monitoring mode using the positive ion mode. The method validation parameters are summarized in Table 17.

Table 17: Summary of bioanalytical method validation for quantification of landiolol and its metabolites in human whole blood

Parameter	Landiolol	Landiolol-M1	Landiolol-M2
Internal Standard	$^{13}C_4$-Landiolol	$^{13}C_4$-Landiolol-M1	$^{13}C_4$-Landiolol-M2
Calibration range [ng/mL]	0.222 – 111	2.78 – 1390	0.222 – 111
QCs (ng/mL)	0.666, 7.50, 95.0	8.34, 93.9, 1190	0.666, 7.50, 95.0
Between-run precision (%CV)	2.5-5.7%	2.8-4.4%	3.0-6.3%
Between-run Accuracy (%)	96.4-102.0%	98.2-102.5%	95.1-100.9%
Matrix	Precipitated human whole blood		
Sample volume (µL)	35		
Short term stability in matrix	24 hours at room temperature		
Long term stability in matrix	66 days at nominal 5 °C 366 days at nominal -20 °C and below -70 °C		
Dilution integrity	up to factor 100		
Max. number of study samples per run	150 matrix samples for evaluation with 2 sets of calibration standards 50 matrix samples for evaluation with 1 set of calibration standards		

Source: LANDI-PED_Validation Report VAL-B12117
Abbreviations: QCs: Quality Controls; CV: Coefficient of Variation

The LC-MS/MS method used to measure landiolol and its metabolites in human whole blood was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation Guidance and reported under validation report number AN-99716. Incurred sample reproducibility (ISR) was assessed by re-analyzing 10 out of the 78 study samples (approximately 12.8% of the sample size). All ISR samples met the acceptance criterion (100%) for Landiolol and Landiolol-M1, 9 of 10 ISR samples met the acceptance criterion (90%) for Landiolol-M2.

15. Study/Trial Design

Not applicable

16. Efficacy

Not applicable.

17. Clinical Safety

Not applicable.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

Not applicable.

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

Not applicable.

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the Applicant's draft PI (Table 18). 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 18. Key Labeling Changes and Considerations

Full PI Sections [1]	Change/Rationale
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	A new indication for the short-term reduction of ventricular rate in pediatric patients with supraventricular tachycardia has been added.
2 DOSAGE AND ADMINISTRATION	Recommended dosage in pediatric patients with normal cardiac function have been added. A note that there is no data to guide dosage recommendations in pediatric patients with impaired cardiac function was added.
4 CONTRAINDICATIONS	No change.
5 WARNINGS AND PRECAUTIONS	No substantive changes.
6 ADVERSE REACTIONS	This section was updated to include adverse reactions in pediatric patients from the clinical trial.
7 DRUG INTERACTIONS	No change.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Section 8.4, Pediatric Use was updated to describe the new pediatric indication and to describe the evidence supporting the indication.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	No substantive changes.
12 CLINICAL PHARMACOLOGY	Pharmacokinetic data in pediatric patients has been included.
13 NONCLINICAL TOXICOLOGY	No change.
14 CLINICAL STUDIES	No change.
17 PATIENT COUNSELING INFORMATION	N/A
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	NDC number has been updated to reflect a change in ownership.

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

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information

24. Postmarketing Requirements and Commitments

No new PMRs or PMCs are warranted.

25. Financial Disclosure

Table 19. Covered Clinical Studies: [LANDI-PED]

Was a list of clinical investigators provided:	Yes ✓	No ☐ (Request list from Applicant)
Total number of investigators identified: 105		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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)): This section is not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ✓ (Not applicable)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ✓ (Not applicable)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason:	Yes ☐	No ✓ (Not applicable)

Abbreviation: FDA, Food and Drug Administration

26. References

1. Anderson, D and Y Zheng 2025, Division of Quality and Microbiology Review: Rapiblyk (Landiolol): Reference ID 5678713.

2. Ashraf M, Collier SA. Junctional Ectopic Tachycardia. [Updated 2025 May 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560851/

3. Batra AS, Silka MJ, Borquez A, Cuneo B, Dechert B, Jaeggi E, Kannankeril PJ, Tabulov C, Tisdale JE, Wolfe D; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology, Council on Basic Cardiovascular Sciences, Council on Cardiovascular and Stroke Nursing, Council on Genomic and Precision Medicine, and Council on Lifelong Congenital Heart Disease and Heart Health in the Young. Pharmacological Management of Cardiac Arrhythmias in the Fetal and Neonatal Periods: A Scientific Statement

From the American Heart Association: Endorsed by the Pediatric & Congenital Electrophysiology Society (PACES). Circulation. 2024 Mar 5;149(10):e937-e952. doi: 10.1161/CIR.0000000000001206. Epub 2024 Feb 5. Erratum in: Circulation. 2024 Mar 19;149(12):e996. doi: 10.1161/CIR.0000000000001226

4. Borquez AA, Williams MR. Essentials of Paroxysmal Supraventricular Tachycardia for the Pediatrician. Pediatric Annals. 2021;50(3):e113-e120. doi:10.3928/19382359-20210217-01.

5. Henning A, Krawiec C. Sinus Tachycardia. [Updated 2023 Mar 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553128/

6. Michel-Behnke I, Müller M, Stiller B, Kriebel T, Kanaan M, Környei L, Mai M, Gebauer R, Meier J, Roses-Noguer F, Unger M, Schlager S, Charu C, Klade C, Krejcy K, Ackerl J, Krumpl G. Landiolol is effective and safe in paediatric supraventricular tachycardia: evidence from a European prospective multicentre open-label phase III study (LANDI-PED). Europace. 2025 Feb 5;27(2):euaf025. doi: 10.1093/europace/euaf025.

7. Nizami Z, Garcia P, Ahuja P et al. Supraventricular tachycardia in children. Progress in Pediatric Cardiology. 2024; 76. https://doi.org/10.1016/j.ppedcard.2024.101771

8. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. Europace. 2019 Feb 1;21(2):194-207. doi: 10.1093/europace/euy128.

9. Patti L, Horenstein MS, Ashurst JV. Supraventricular Tachycardia. [Updated 2025 Feb 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441972/

10. Sasikumar N, Kumar RK, Balaji S. Diagnosis and management of junctional ectopic tachycardia in children. Ann Pediatr Cardiol. 2021 Jul-Sep;14(3):372-381. doi: 10.4103/apc.apc_35_21. Epub 2021 Aug 20.

11. Sheldon RS, Grubb BP 2nd, Olshansky B, Shen WK, Calkins H, Brignole M, Raj SR, Krahn AD, Morillo CA, Stewart JM, Sutton R, Sandroni P, Friday KJ, Hachul DT, Cohen MI, Lau DH, Mayuga KA, Moak JP, Sandhu RK, Kanjwal K. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015 Jun;12(6):e41-63. doi: 10.1016/j.hrthm.2015.03.029.

27. Review Team

Table 20. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Mayam Changi, PharmD
Nonclinical reviewer	N/A
Nonclinical team leader	N/A
OCP reviewer(s)	Anusha Ande, PhD
OCP team leader(s)	Elly Moon, PharmD
Clinical reviewer	Ann Punnoose, MD
Clinical team leader	Fortunato Senatore, MD, PhD, FACC
Biometrics reviewer	Ququan (Cherry) Liu, PhD
Biometrics team leader	Jennifer Clark, PhD
Cross-discipline team leader	Fortunato Senatore, MD, PhD, FACC
Division director (pharm/tox)	N/A
Division director (OCP)	N/A
Division director (OB)	N/A
Deputy Division director (clinical-Signatory authority)	Charu Gandotra, MD, MS, FACC, FASE
Associate Director for Labeling	Michael V. Monteleone, MS, RAC

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

Table 21. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	N/A
Microbiology	Yan Zheng, PhD/ David Anderson, PhD
OPDP	Meena Savani, PharmD
OSI	N/A
OSE/DEPI	Margie R. Goulding, PhD/ Monique Falconer, MD, MS/ Christian Cao, MPAS,PA-C
OSE/DMEPA	Julie Neshiewat, PharmD, MS, BCPS, CPH/ Nicole Iverson, PharmD, BCPS
OSE/DRISK	N/A
DPMH	Sonaly McClymont, MD,/ Shetarra Walker, MD

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

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/s/

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CHARU GANDOTRA
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