Clinical Study Report

1. Title page

Study title	A retrospective-prospective observational study to assess landiolol utilization patterns in patients with supraventricular tachycardia, for rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter, for short-term control of the ventricular rate, or for non-compensatory sinus tachycardia
Medicinal Product	Landiolol 300 mg powder for solution for infusion (trade names Rapibloc, Raploc, Landiobloc, Runrapiq)
Indications	• *Supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable* • *Non-compensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention*
Marketing authorization holder	Amomed Pharma GmbH, a member of the AOP Orphan Group
EU PAS register number	EUPAS1000000297
Phase of development	Non-interventional study
Study period	Study start: 09 Jul 2020 (start of data collection) Study completion: 31 Dec 2023 (end of data collection)
Version	V1.0
Date of Report	17 Sep 2024
This clinical study was conducted in compliance with local laws and guidelines. The report was written in accordance with ICH E3 and NI-PASS guidelines.	
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Signature Page

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

[redacted]

Principal investigator	Date	Signature

[redacted]

For the sponsor's signatory	Date	Signature

2. Abstract

Marketing authorization holder: Amomed Pharma GmbH represented by [redacted] from AOP Orphan Pharmaceuticals GmbH	Individual Study Table Referring to Part of the Dossier Volume	*(For National Authority use only)*
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Study title

A retrospective-prospective observational study to assess landiolol utilization patterns in patients with supraventricular tachycardia, for rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter, for short-term control of the ventricular rate, or for non-compensatory sinus tachycardia

Keywords

Landiolol, supraventricular tachycardia, heart rate control, real-world data

Rationale and background

Intravenous landiolol was developed in Japan and has been used there for more than 20 years in critical care. Since its introduction to the European market in 2017, limited real-world data on its use has been collected. This non-interventional study (NIS) aimed to evaluate landiolol's utilization patterns, patient characteristics, effectiveness, and safety in everyday medical practice across Europe.

Objectives

Primary objective:

- to characterize the drug utilization patterns in patients who were treated with landiolol according to the Summary of Product Characteristics (SmPC)

Secondary objectives:

- to evaluate effectiveness of landiolol treatment in a real-world setting
- to evaluate characteristics of patients treated with landiolol intravenously in a real-world setting
- to evaluate the safety of patients treated with landiolol intravenously in a real-world setting to facilitate life-cycle risk-benefit profiling
- to assess length of intensive/ emergency care and hospital stay
- to survey the major cardiac outcome of patients treated with landiolol up to 180 days

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Study design

This retrospective-prospective NIS was designed to monitor the drug utilization patterns, baseline characteristics, effectiveness and safety real-world data in patients treated with landiolol. Patients were recruited from perioperative, postoperative, intensive care or emergency care units, where medical staff was trained and qualified for the administration of landiolol and where patients were adequately monitored during the treatment. To prevent a selection bias, a waiver for retrospective routine data collection without prior consent was granted for patients who died or were otherwise incapable of consenting during hospitalization. The study did not interfere with the standard patient care, and the protocol did not require any study visits or specific diagnostic interventions. Patients' visit schedules followed local standard of care with additional visits required at the treating physician's discretion. A patient completed the study either upon discharge from hospital (Visit 4) or by reaching the 6-month follow-up visit (Visit 5 was optional). However, this period could be shortened if patient was lost to follow-up or had died. No additional information was collected solely for the purpose of this study.

Study population and sample size

Male or female patients aged ≥ 18 years old who received landiolol according to the SmPC, as determined by the treating physician, were included in the study. All participants were to be informed about the study and sign the informed consent, if able to give consent. Patients who were incapable for consenting during hospitalization were informed of the study after discharge. Every effort was made to inform the patient. In all countries except Austria, a waiver was in place to allow retrospective data collection without prior consent of patients who died or were otherwise incapable of consenting during hospitalization. In Austria, such a waiver only applied to patients who died during hospitalization.

Sample size:

Enrolled: 450 patients, of which 244 completed the 6-month follow-up period

Analyzed: 449 patients, of which 244 completed the 6-month follow-up period

Study centers

A total of 20 sites across 8 EU countries participated in the study. Of these, 17 sites enrolled at least 1 patient. The sites were located in Austria (4), Germany (2), Netherlands (1), Poland (5), Hungary (2), Slovenia (1), Greece (3), and Czech Republic (2).

Coordinating physician

[redacted]

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Study endpoints and data sources

Landiolol utilization patterns:

- total dose infused
- duration of infusion
- starting dose
- minimum dose
- maximum dose
- preferred route of application (central or peripheral line)
- reason for discontinuation

Patient characteristics, including medical history, reason for landiolol use, left ventricular ejection fraction and use of concomitant medications

Efficacy data assessed within 4 hours after landiolol discontinuation based on:

- Percentage of patients with a heart rate (HR) control ≤ 110 beats per minutes (bpm) or 20% less than baseline
- Percentage of patients with a HR control ≤ 90 bpm
- Percentage of patients who recover the normal sinus rhythm
- Proportion of patients requiring additional pharmacological or electrical cardioversion for rhythm control during hospital stay

Safety data up to 180 days after landiolol initiation:

- Adverse events (AEs) concerning number of patients and events, incidence rate, seriousness, intensity and relationship to study drug
- AEs requiring discontinuation of the treatment
- AEs requiring treatment with specific therapy
- Length of Intensive Care Unit (ICU)/ Emergency Care Unit (ECU) and hospital stay
- Major adverse cardiac events (MACE) by type: transient ischemic attack or ischemic stroke, myocardial infarction (STEMI and NSTEMI), cardiovascular death, all-cause mortality, unstable angina, hospitalization for heart failure, de-novo atrial fibrillation requiring specific treatment.

Data was to be extracted from various sources - medical records, prescription records, laboratory or cardiac assessment reports, or routine interviews of patients - and entered into an electronic data capture (EDC) system at the time of enrolment and whenever possible in the following 6 months.

Results:

A total of 450 patients were enrolled in the study after being treated with intravenous landiolol, mostly in the ICU (51%), ECU (40%) and normal hospital ward (9%). One patient was excluded from the statistical analysis due to missing landiolol usage data and insufficient data for secondary endpoints. The mean (± SD) age of patients was 69.6 ± 12.0 years and more male than female patients (59% vs 41%) were included. The study enrolled predominantly Caucasian patients (441/449, 98%); the remaining patients were Asian (8/449, 2%). The mean (± SD) body mass index (BMI) was 28.6 ± 6.1 kg/m^2. Regarding the indication for landiolol treatment, 73% (328/449) of patients were treated with landiolol for atrial fibrillation, followed by non-compensatory sinus tachycardia affecting 10% (47/449) of patients and atrial flutter affecting 9% (42/449) of patients. The mean (± SD) HR at baseline in the whole study population was 132.4 ± 26.4 bpm. At the start of landiolol treatment, 10% (44/449) of patients suffered from sepsis, 9% (41/449) from acute myocardial infarction and 15% (69/449) from heart failure. Among 449 patients treated with landiolol and analysed in the study, 20 subjects received 2 treatments each and 4 subjects received 3 treatments each (477 treatments in total). The landiolol utilization patterns observed in this study were as follows:

	All treatments
Total dose infused [mg]	300 (0.01-11,477)
Infusion duration [h]	8.9 h (3 min – 20 days)
Lowest infusion rate [µg/kg/min]	4 (0-100)
Highest infusion rate [µg/kg/min]	10 (1-100)
Preferred route of application [n, %]	
Central line	253 (53%)
Peripheral line	215 (45%)
Reason for discontinuation [n, %]	
Treatment effective	321 (67%)
Adverse event	9 (2%)
All-cause death*	10 (2%)

For all usage parameters median and range (minimum and maximum) are shown. *not related to landiolol treatment

74% (333/449) of patients achieved HR control ≤ 110 bpm or 20% less than baseline and 50% (224/449) of patients achieved ≤ 90 bpm within 4 hours after landiolol discontinuation. The highest success rates (HR ≤ 110 bpm or 20% less than baseline) were observed in the ICU (83%), for non-compensatory sinus tachycardia (89%), and in patients with myocardial infarction (83%). In 42% (187/449) of patients, landiolol use was associated with a conversion to sinus rhythm during 4h of landiolol treatment discontinuation. 42% (190/449) patients required additional pharmacological or electrical cardioversion for rhythm control. For those who survived, the mean (± SD) length of stay in the ICU, ECU and hospital was 17.3 ± 21.3, 4.6 ± 6.1 and 14.3 ± 18.5 days, respectively. A total of 123 AEs occurred in 79/449 (18%) patients. Of these AEs, 56 were considered serious AEs (SAEs). Within 6 months of landiolol treatment, 113 MACEs were reported in 112 patients, including 110 deaths. None of the AEs or MACEs was assessed to be related to the landiolol treatment.

Conclusions

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Across Europe, patients are being administered intravenous landiolol in line with approved labeling and the European Society of Cardiology (ESC) guidelines. Dosing of landiolol in clinical routine practice corresponded to the recommendations in the SmPC. The median duration of landiolol infusion was 8.9 hours, with a median peak dose of 10 µg/kg/min. This usage reflects the high number of patients with cardiac dysfunction in this study and is consistent with the recommendations in the SmPC which recommends dose of 1-10 µg/kg/min. Landiolol provided HR control in the majority of patients while minimally impacting systemic hemodynamics. Tachycardia was well managed by landiolol intervention across supraventricular tachycardia subtypes. Landiolol was generally well tolerated, with a low incidence of hypotension and bradycardia, highlighting its favorable safety profile and the effectiveness of the risk management measures. There were no AEs or MACEs related to landiolol and no new safety concerns were identified. These findings have no impact on the benefit-risk ratio of the product. By reflecting a more comprehensive experience on the drug use at a larger scale, this real-world data strengthens the evidence base for landiolol in patients with tachycardia of various origin, in different hospital settings, and with other concurrent illnesses or on other concurrent medications.

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4. List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
BPM	Beats per Minute
ECU	Emergency Care Unit
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
NSTEMI	Non-ST-Elevation Myocardial Infarction
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STEMI	ST Elevation Myocardial Infarction
V	Visit

Note: Abbreviations used only in tables are explained in the corresponding table legend and are not included in this list.

5. Ethics

5.1. Independent Ethics Committees or Institutional Review Board

The Central Ethics Committee responsible for this study was the Ethics Committee of the Medical University of Vienna. The Committee approved the study protocol, Informed Consent forms (ICFs), and other relevant documents before site initiation. Protocol amendments were also approved by the respective ethics committees.

A list of all ethics committees consulted is given in Appendix 13.1.3.

5.2. Ethical conduct of the study

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and its full amendments, and in the general spirit of ICH-GCP Good Clinical Practice Guidelines – both in their currently adopted versions.

5.3. Informed consent

Patients who were deemed suitable by their treating physicians for treatment with landiolol for their underlying condition and fulfilled eligibility criteria were identified as potential patients for this study. Data was to be collected only after patient provided written informed consent, if able to give consent. Patients who were incapable for consenting during hospitalization were informed of the study after discharge. Every effort was made to inform the patient. In all countries except Austria, a waiver was in place to allow retrospective data collection without prior consent of patients who died or were otherwise incapable of consenting during hospitalization, taking into consideration an emergency situation. In Austria, such a waiver only applied to patients who died during hospitalization.

A sample patient consent form is provided in Appendix 13.1.3.

5.4. Insurance

A study-related patient insurance was not required for this observational NIS.

6. Responsible parties

For a list of all the investigators with their affiliations, see Appendix 13.1.4.

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7. Introduction

7.1. Background

Tachycardia is a common term used to describe abnormal heart rates (HR) of more than 100 bpm which cause the heart to beat quickly and sometimes irregularly. Tachycardias are classified into different types according to the cause and the part of the heart causing the fast HR (Mayo Clinic website). Originating from the sinoatrial node, non-compensatory sinus tachycardia refers to an elevated HR that occurs without a physiological reason such as exercise, fever, or stress. It may be caused by sepsis, autonomic dysfunction, hyperthyroidism, and certain medicines. Originating at or above the atrioventricular junction, supraventricular tachycardia includes irregular heart rhythms such as atrial fibrillation and atrial flutter. These arrhythmias are the most common type of pathological tachycardia. In atrial fibrillation, the atria beat irregularly, while in atrial flutter, the atria beat regularly, but faster than usual and more often than the ventricles. Finally, ventricular tachycardia is a type of fast heart rhythm originating from the ventricles and is associated with heart conditions such as myocarditis, myocardial infarction, heart failure, and certain drugs, especially those that affect the heart's electrical activity. When left untreated, some forms of tachycardia can lead to serious health problems such as heart failure, stroke or sudden cardiac death.

Cardiac arrhythmias are common in the ICU, and may either be the primary reason for admission or a complication of an existing medical condition. Both the European Society of Cardiology and the American College of Cardiology recommend beta-blockers as a first-line therapy in the management of arrhythmias because of their rapid onset of action and effectiveness at high sympathetic tone (Hindricks et al., 2021; Joglar et al., 2024). Nevertheless, the choice of drug and target HR will depend on the patient characteristics, symptoms, left ventricular ejection fraction (LVEF) value, and hemodynamics. Combination therapy may be required, for example, in heart failure patients with reduced LVEF. In hemodynamically unstable patients, urgent cardioversion should be considered. Beta-blockers are also a treatment option for non-compensatory sinus tachycardia (albeit with limited efficacy) (Ahmed et al., 2022) and ventricular tachycardia (Priori et al., 2015). Landiolol, an intravenous ultrashort-acting beta-blocker, is ideal for acute rate control (Syed, 2018;

Nasoufidou et al., 2024). With a very short elimination half-life of approximately 4 min, landiolol is easy to use in acute settings because any adverse effects can be quickly managed by tapering the dose or discontinuing treatment. Moreover, when compared to other beta-blocker therapies, it presents certain advantages, such as a potent negative chronotropic effect but a limited negative inotropic effect, particularly beneficial for patients who already have weakened heart function.

7.2. Rationale

Landiolol was developed in Japan (tradename in Japan: Onoact®) and has been used there for more than 20 years in critical care. Landiolol was launched in the European market in 2017 (trade names: Rapibloc, Raploc, Landiobloc, Runrapiq) for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable, as well as for non-compensatory sinus tachyarrhythmia where, in the physician's judgment, the rapid HR requires specific intervention. However, little real-world data has been obtained on landiolol use in European countries. Real-world evidence derived from a NIS ought to provide important information on product utilization and demonstrate value over a product's lifecycle and facilitate benefit-risk assessment. This post-marketing study, conducted voluntarily by Amomed, aimed to monitor the drug utilization patterns, patient characteristics, effectiveness, and safety in routine clinical practice across 8 European countries.

7.3. Milestones

Start of data collection and end of data collection are defined in Module VIII of the Good pharmacovigilance practices. Start of data collection is the date from which information on the first study subject was first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction started. End of data collection is the date from which the analytical dataset was completely available.

A list of all protocol amendments is provided in section 9.10.

Milestone	Planned date	Actual date	Comments
Start of data collection	Jun 2020	09 Jul 2020	
End of data collection	Dec 2023	31 Dec 2023	
Registration in the EU PAS register	Aug 2024	03 Sep 2024	
Database lock	Mar 2024	7 Mar 2024	
First protocol approval by EC	May 2020	10 Jun 2020 (CSP V2.0)	conditional approval of V1.0 on 26 May 2020
First draft of the study report	May 2024	22 Jul 2024	

8. Study Objectives

Primary objective

- To characterize the drug utilization patterns in patients who were treated with landiolol according to the SmPC

Secondary objectives

- To evaluate effectiveness of landiolol treatment in a real-world setting
- To evaluate characteristics of patients treated with landiolol intravenously in a real-world setting
- To evaluate the safety of patients treated with landiolol intravenously in a real-world setting to facilitate life-cycle risk-benefit profiling
- To assess length of intensive/ emergency care and hospital stay
- To survey the major cardiac outcome of patients treated with landiolol up to 180 days

9. Research methods

9.1. Study design

This study was a retrospective-prospective, multicenter, multinational, observational non-controlled, post-authorization study in patients treated with landiolol. It was designed to assess drug utilization pattern, effectiveness, safety, patient characteristics and follow-up data on MACEs up to 180 days. Patients were enrolled after their physicians had already deemed them suitable for intravenous treatment with landiolol. Patients who were incapable for consenting during hospitalization were informed of the study after discharge. Every effort was made to inform the patient. Informed consent was to be obtained before entering data into the study database. To prevent a selection bias, a waiver for retrospective routine data collection without prior consent was granted for patients who died or, in all countries except Austria, were otherwise incapable of consenting during hospitalization. In Austria, for those who were incapable of consenting during hospitalization, all efforts have been made to obtain informed consent after discharge but prior to data collection. Given the nature of the observational study, there were no study visits mandated by the study protocol. Patients' visit schedules were to follow local standard of care with additional visits requested at the treating physician's discretion. For each patient, landiolol exposure and its effect on cardiac rhythm and rate control were to be assessed. Furthermore, MACEs were to be collected up to 6 months after the first administration of landiolol as long as possible during the patient's re-visits scheduled according to standard of care. A patient completed the study after being discharged from hospital or by reaching the 6-month follow-up visit (optional). No additional information must be collected solely for the purpose of this study. The study design is depicted in Figure 1.

The effective protocols are included as Appendix 13.1.1.

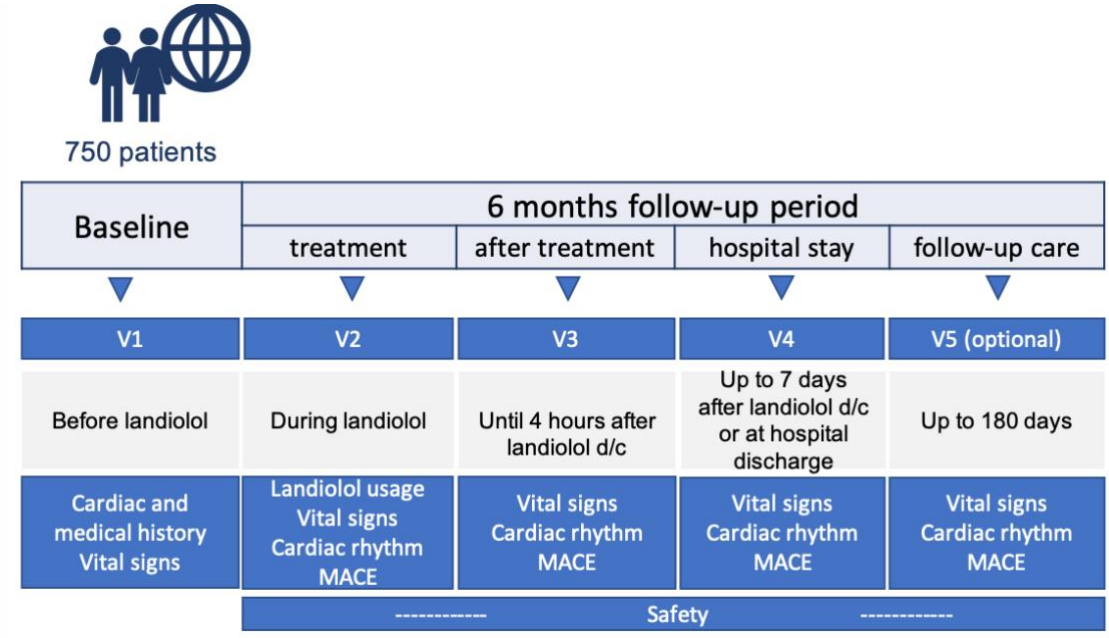

Figure 1: Study design. AEs, with a focus on MACEs, were to be collected up to 180 days (for as long as information was available). d/c = discontinuation.

9.2. Setting

Patients were enrolled in acute cardiac perioperative, postoperative, intensive care or emergency care settings, where medical staff was trained and qualified for the administration of landiolol and where patients were adequately monitored during the treatment. The anticipated duration for this study was approximately 36 months, assuming a 30-month enrolment period and a 6-month follow-up period. The duration of data collection for the individual patient was planned to be approximately 6 months. However, this period could have been shortened if patient was lost to follow-up or died. We expected to obtain follow-up data covering the full 6-month period for at least 250 patients.

9.3. Study population

The following inclusion criteria were applied:

1. Male or female patients
2. Aged ≥ 18 years old
3. Patients who received landiolol for the treatment of supraventricular tachycardia, the rapid control of ventricular rate in atrial fibrillation or atrial flutter, other circumstances where the short-term control of the ventricular rate with a short acting agent is desirable, or non-compensatory sinus tachycardia
4. All patients were to be informed about the study and consent as soon as they were capable of consenting. All countries except Austria (protocols V3.0 and V3.1)*:* Waiver for retrospective routine data collection without prior consent was given to data of patients who died during the hospitalization or were not capable of consenting during hospitalization. In Austria (protocol V5.0): Patients who were not capable of consenting during hospitalization were be informed of the study after discharge. Waiver for

retrospective routine data collection without prior consent was given to data of patients who died during the hospitalization.

Sites were asked to include all patients in this study who were deemed suitable for landiolol therapy.

9.4. Variables

As this was a retrospective-prospective, observational study, information collected from the data source materials were to be directly transferred into variables, namely patient medical information collected in the electronic case report form (eCRF). A blank eCRF is shown in Appendix 13.1.2. The study protocol did not assign treatments, nor did it dictate what medical information should be entered into patient charts. Rather, each participating site provided and documented patient care and outcomes according to usual care, physician discretion and local practice standards. Thus, study variables may not be available for all patients at all time points, if data were not recorded in the chart as per routine medical care.

The data that was to be collected by the investigator during patient visits is shown in Table 1.

Table 1: Visit schedule and data collection.

Visit No.	**V1[1]**	**V2[2]**	**V3[2]**	**V4[2]**	**V5[2,3]**
Time Points	**Before landiolol treatment**	**During landiolol treatment**	**Within 4 hours after landiolol d/c**	**Up to 7 days after d/c or at hospital discharge**	**Follow-up visits as per standard of care up to 180 days**
Informed consent		---------- x ----------			
Inclusion criteria	---------- x ----------				
Allocation of Subject No	---------- x ----------				
Retrospective or Prospective Data Collection					
Demographic Data	x				
Cardiac and medical history	x				
Therapeutic indication	x				
Vital signs[4]	x	x	x	x	x
Cardiac monitoring or 12 lead ECG[5]	x	x	x	x	x
LVEF and left atrial size[6]	x	x	x	x	x
Landiolol usage		x			
MACE		x	x	x	x
AE monitoring		x	x		
Late ADRs				x	x
Hospital stay[7]	x	x	x	x	x
Prior and concomitant intervention	x	x	x	x	
Prior and concomitant medication	x	x	x	x	x

d/c = discontinuation; ADR = adverse drug reaction; ECG = electrocardiogram.

[1]During data cleaning, it was established that the "before landiolol treatment" period should be restricted to within 24 hours prior to treatment.
[2]For Visits 2-5, a minimum of one data entry per time point is requested as far as available from routine clinical data. However, multiple data entries per visit are recommended during the specified time-window, if clinically relevant.
[3]Visit 5 (optional) was to be performed within 6 months of landiolol treatment. This follow up could be conducted via phone call or in the hospital, depending on the patient's condition.
[4]Vital signs include heart rate expressed as beats per minute (bpm), systolic and diastolic blood pressure (in mmHg), body temperature (in °Celsius only during hospital stay, Visit 1 to Visit 3), peripheral/ blood oxygen saturation (in %; only during hospital stay, Visit 1 to Visit 3).
[5]Cardiac monitoring/ ECG: rhythm, rate, other abnormalities.
[6]LVEF and atrial size assessed by echocardiography or other imaging if available - can be obtained from assessment performed anytime during hospital stay.
[7]Length of hospital stay in any hospital setting.

9.4.1. Landiolol treatment

The decision to initiate treatment with landiolol was guided by the treating physician and should be in accordance with the approved labelling and the SmPC of the product. All sites received the latest effective version of the SmPC and qualified staff of the MAH ensured that the site staff was updated in a case that a new version of SmPC was released. The SmPC is provided in Appendix 13.1.5.

9.5. Data sources and measurement

Subjects visited the hospital per standard of care of underlying medical condition for the regular or emergency visits during their treatment according to local clinical practice. The assessments conducted during these visits were according to clinical practice.

Data of patients treated with landiolol before site activation was to be collected retrospectively dated from the time of site activation and/or prospectively to end of study. Data of patients treated with landiolol after site activation was to be collected retrospectively (V1 baseline data) and prospectively (V2-V5 data) from the date of receipt of informed consent throughout the whole study.

Data was to be extracted from various sources - medical records, prescription records, laboratory or cardiac assessment reports, or routine interviews of patients - and entered into the eCRF by the site staff of the treating physician assigned to this study.

The primary endpoint of this study was landiolol utilization pattern. The site staff was requested to enter the following information in the eCRF: start date and time of landiolol treatment, starting infusion rate, lowest infusion rate, highest infusion rate, total dose infused, route of application (central or peripheral line), reason for dose change (if selected), end date and time of treatment, and reason for discontinuation of treatment. "Total dose infused" was calculated by the site staff before entering it into the eCRF. Multiple data entries for landiolol usage were permitted in case of retreatment.

9.6. Bias

Patient selection bias is addressed in section 9.1. Other bias, such as those related to the accuracy, consistency, and completeness of data, were minimized by means of training sessions, investigator meetings, remote and on-site data monitoring, source data verification, and data cleaning.

Treating physicians and study coordinators were trained on the protocol version for that country, study flow, electronic data capture (EDC) system, documentation, site responsibilities and expectations, and any applicable study processes. The MAH, project lead, or their designee trained each site during the site initiation visit. Ongoing site management occurred throughout the entire duration of the study by qualified staff of the MAH. Additional trainings were performed in case additional points needed to be clarified with the site team, and documented in the site training log/ monitoring visit reports. Two investigator meetings took place to standardize performance. Otherwise, information was circulated via regular newsletters (quarterly, or upon particular milestones) and email.

Remote data monitoring was conducted during the lifecycle of the study to identify missing or unclear data in the EDC system and issue queries. The remote project manager and data manager closely monitored the patient recruitment and data collection to ensure data quality requirements were being met. In case of increasing queries at a specific site or implausible data entry bearing difficulties to clean remotely by the CDM team, an onsite monitoring was to be scheduled to follow-up with the site and review source documents for verification of data recorded in the eCRFs. As for on-site monitoring, monitoring visits and site check-ins (i.e. not triggered based on data quality) were performed.

The main focus of data cleaning was the primary endpoint “landiolol usage”. Extensive cross-checking was carried out to ensure the consistency between related measures in the eCRF. For example, any “total dose infused” values that fell outside the possible range - given the minimum and maximum doses, treatment duration and patient’s weight - were flagged for further review. All sites were encouraged to use a common excel sheet with a dose calculator to assist in the total dose calculation.

9.7. Data protection

The primary risk for patients in NIS is breach of data privacy. The data was stored and processed in pseudonymized form (i.e., without reference to the participant’s name) by means of a unique subject identification number. Data access was restricted to authorized personnel, with measures in place to prevent data loss. All applicable data protection laws were observed. For data exports, datasets were encrypted and protected by the use of passwords.

9.8. Data transformation

AEs, medical history, and concomitant medication data were coded using the Medical Dictionary for Regulatory Activities (MedDRA 26.0). Concomitant medications were coded by using the World Health Organisation (WHO) Drug Dictionary (WHO Drug Global B3/C3-format December 1, 2023). All other data was directly exported from the eCRF to the study statistician, without any further processing.

9.9. Statistical methods

A Statistical Analysis Plan (SAP) was prepared by the study statistician and, after approval by the Sponsor, was issued as a separate document on 26 Feb 2024. It provided detailed methods for the analyses outlined below. The final version of the SAP is included in Appendix 13.1.6. Database lock took place on 7 Mar 2024.

9.9.1. Sample size

Approximately 750 patients treated with landiolol were planned to be enrolled over a period of 3 years at approximately 24 sites across Europe. Of those, 250 patients were expected to complete the entire 6-month follow-up period. No formal sample size calculation was performed. Based on the incidence of disease and observational nature of the study, the sample size number was considered adequate to investigate the objectives of the study.

9.9.2. Statistical methods

As per SAP, all subjects enrolled in the study were to be included in the analysis, and no other analysis populations were defined. In this study, no protocol deviations were to be considered in the definition of the analysis set.

For all visits, the eCRF fields medical history, AEs, MACEs, concomitant medication and concomitant intervention allowed multiple data entries. In contrast, other fields permitted only one data entry, which would overwrite any previous information. The exceptions were the data for Visit 2 (in the case of re-treatment with landiolol) and for the facultative Visit 5.

The following subgroups were defined in the SAP:

- Hospital setting at time of the arrhythmia onset - ICU, ECU, postoperative monitoring care, normal hospital ward, outpatient clinic, or other [identified by “setting of patient admission” at Visit 1]
- Indication - non-compensatory sinus tachycardia, atrial fibrillation, atrial flutter, short-term control of the ventricular rate, other supraventricular tachycardia, or other [identified by “rhythm disorder requiring landiolol treatment” at Visit 1]
- Presence of sepsis at time of landiolol treatment start – patients with sepsis or patients without sepsis [identified by medical history events which were coded as sepsis or septic shock and were still ongoing at treatment start, in addition to patients with sepsis reported in “condition directly associated with rhythm disorder”]
- Presence of heart failure at time of landiolol treatment start - patients with heart failure or patients without heart failure [identified by medical history events which were still ongoing at treatment start coded as cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive and LV failure, in addition to patients with acute decompensated heart failure reported in “condition directly associated with rhythm disorder”]
- Presence of myocardial infarction at time of landiolol treatment start - patients with myocardial infarction or patients without myocardial infarction [identified by “myocardial infarction” reported in medical history and ongoing at treatment start, in addition to patients with (peri-)myocardial infarction reported in “condition directly associated with rhythm disorder”]
- Concomitant medication – patients on antiarrhythmic agents administered less than 7 days before treatment with landiolol (Yes/No) and patients on inotropic agents during treatment with landiolol (Yes/No) [identified by corresponding ATC codes reported in concomitant medication]
- Concomitant treatment – patients undergoing electric cardioversion (Yes/No) or cardiac ablation (Yes/No) before the treatment with landiolol [identified in medical history by PT term].

The primary endpoint was to be presented by subgroups (hospital setting, indication, sepsis, heart failure, myocardial infarction, concomitant medication and concomitant treatment) and overall.

For exploratory dose-response analysis, dose categories for the administered medicinal product have been defined based on the quantiles of the infused total dose distribution as follows:

- dose in the interval [Minimum, Q1)
- dose in the interval [Q1, Median)
- dose in the interval [Median, Q3)
- dose in the interval [Q3, Maximum]

9.9.3. Missing values

Considerable amounts of missing data are to be expected in observational studies. Missing data was not to be imputed. However, during the analysis, it was decided to impute death events which were accidently not ticked as AE or MACE. The missing date of death was imputed by using the last entry in eCRF (see section 10.1 of the statistical report).

9.9.4. Sensitivity analyses

Not applicable.

9.9.5. Quality control

An EDC system was used to capture study data at the site. All data collected via the eCRF was to be reviewed for clarity and completeness through online edit checks and offline checks run by the clinical data manager according to the data validation plan. For all identified discrepancies, the clinical data manager was to raise a query in the EDC application. The appropriate site personnel answered the queries in the eCRF, which were audit trailed by the EDC application.

9.10. Changes in the conduct of the study or planned analyses

9.10.1. Amendments to the protocol

The original study protocol (version 1.0) issued on 25 Mar 2020 never became effective. Five protocol amendments were issued, as indicated in Table 2. The first protocol version that came into effect was version 2.0.

Table 2: Initial version and amendments to the study protocol.

Protocol version and date	Amendment	Reason
V1.0; 25.03.2020 (never effective)	Initial release	N/A
V2.0; 28.05.2020 (first effective version)	Added time for obtaining ICF in Table 1 Added race to demographics	To address Austrian EC comments
V3.0; 10.02.2021 (effective in DE, CZ, GR, HU, PL, SI)	Added deferred informed consent for deceased patients and patients not capable of consenting during hospitalization Changed MAH contact	To minimize selection bias at the request of the Austrian EC
V3.1; 17.11.2021 (effective in NL)	Updated MAH address and MAH representative legal entity Updated Biostatistics address and legal entity	Change of address of MAH and MAH representative legal entity

		Change of Biostatistics address and legal entity
V4.0; 04.05.2021 (never effective)	Added definition of patients not capable of consenting Established procedure for informing patients unable to consent during hospitalization	To address Austrian EC comments
V5.0; 08.06.2021 (effective in AT)	Removed waiver for patients not capable of consenting during hospitalization Removed "post-hoc" wording	To address Austrian EC comments

9.10.2. Amendments to the statistical analysis plan
Not applicable.

10. Results

A total of 20 sites across 8 EU countries participated in the study. The sites were located in Austria (4), Czech Republic (2), Germany (2), Greece (3), Hungary (2), Netherlands (1), Poland (5), and Slovenia (1). The following 17 sites enrolled at least 1 patient: Medical University Vienna (AT), University Hospital Graz (AT), Ordensklinikum Linz (AT), Wels Clinic (AT), Institute of Clinical and Experimental Medicine (CZ), Motol University Hospital (CZ), Dresden University Clinic (DE), Konstantopoulio General Hospital (GR), Evangelismos General Hospital (GR), General State Hospital of Nikaia (GR), Semmelweis University Budapest (HU), Medical Center Leeuwarden (NL), Poznan University of Medical Sciences (PL), Poznan Wojewodzki Hospital (PL), Medical University of Warsaw (PL), Wroclaw University Clinical Hospital (PL), and University Medical Centre Ljubljana (SL).

Data collection started on 09 Jul 2020 (first participant entered into eCRF) and ended on 31 Dec 2023.

A statistical report V1.0 was issued by the study statistician on 04 Sep 2024 (see Appendix 13.3).

10.1. Participant disposition

A total of 450 patients were enrolled in the study after being treated with intravenous landiolol. One patient (DE-D01-00045) did not provide the evaluable data for the primary and secondary endpoints analyses, therefore this patient was excluded from the statistical analysis. No AEs were recorded for this patient. All the data available for this patient is provided in section 14 of the statistical report. The number of patients seeking care in the different hospital settings is shown in Figure 2. About 90% of patients were treated with landiolol in critical care units, either in the ICU or ECU. Some participants were transferred between hospital settings during the course of the study (for more details see Table 19). Over the following 6 months, 110 patients died most likely due to the multiple advanced comorbidities, and 92 patients were lost to follow-up. None of the deaths was assessed to be related to the landiolol treatment. A listing of all patients who did not complete the study, either due to death or lost to follow-up, is presented in Appendix 13.2 - disposition.

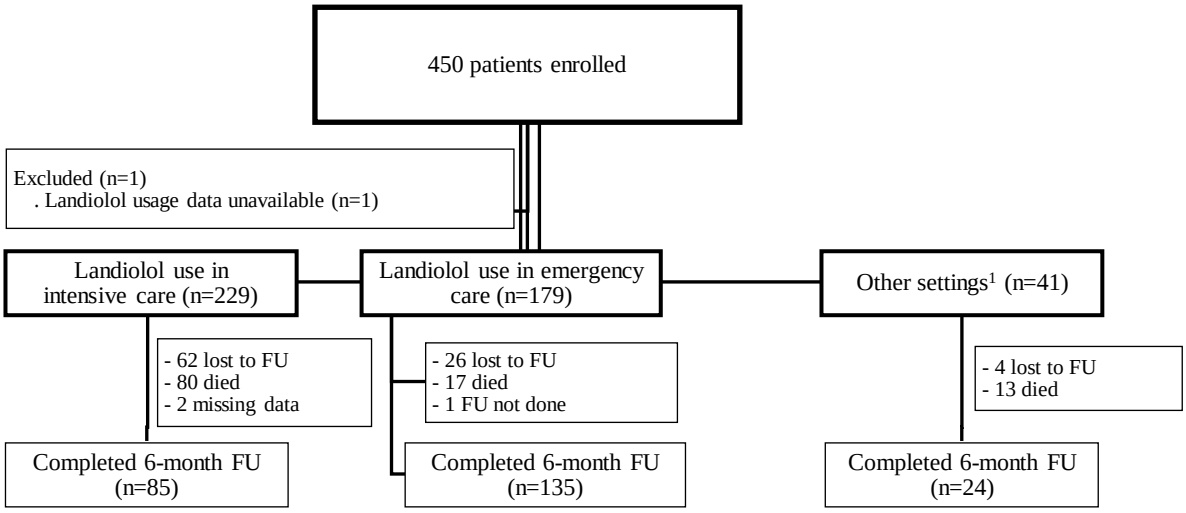

Figure 2: Patient disposition broken down by hospital setting at time of the tachycardia onset. [1]Other settings include normal hospital ward (38 patients), postoperative monitoring care (1), outpatient clinic (1) and other (1). FU = follow up. Source: Statistical Tables 1, 3 and 209.

In this study, a waiver for retrospective data collection without prior consent was granted for patients who died or were otherwise incapable of consenting during hospitalization. Exceptionally, in Austria, such a waiver only applied to patients who died during hospitalization. Patients who were incapable for consenting during hospitalization were informed of the study after discharge. Every effort was made to inform the patient. This waiver was employed to varying extents among the participating countries (Figure 3), covering about 35% of the study population.

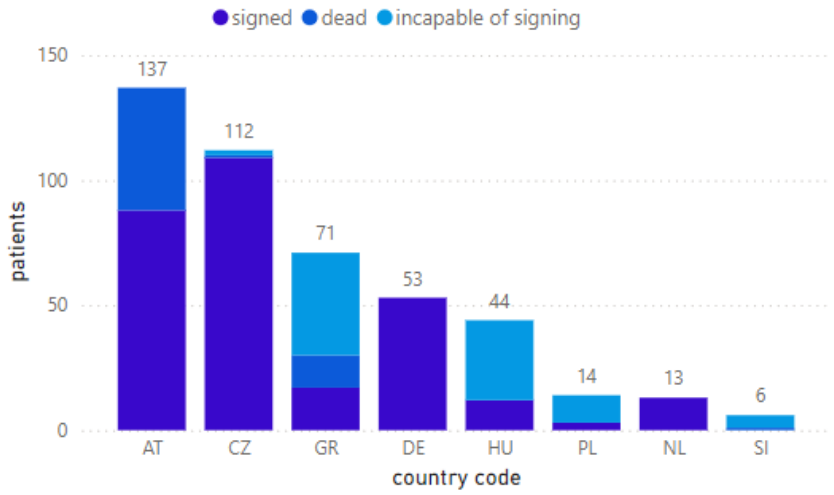

Figure 3: Patient disposition broken down by country and consent status. A waiver for retrospective data collection without prior consent was granted for patients who died or were otherwise incapable of signing the ICF during hospitalization. Source: Statistical Tables 4 and 7. By-patient listing available in Appendix 13.2 – informed consent.

10.2. Protocol deviations

All deviations from the study protocol are listed in Statistical Table 8. In total, 22 protocol deviations were related to the informed consent process (19), eligibility criteria (2), and assessments (1). Of these, 14 were identified as major and 8 as minor by the MAH. All major deviations were related to the informed consent: “failure to obtain signed ICF before inclusion in the study”.

In accordance with the SAP, protocol deviations did not lead to the exclusion of any patient from the analysis.

10.3. Participant baseline characteristics and use of concomitant medications

The study population included 267 (59%) male and 182 (41%) female patients, mostly Caucasians (98%), who were treated with landiolol according to the SmPC (Table 3). Mean (± SD) age was 69.6 ± 12.0 years and mean (± SD) BMI was 28.6 ± 6.1 kg/m^2.

Table 3: Demographics of the study participants

	All patients
N	449
Age [years], mean ± SD	69.6 ± 12.0
BMI [kg/m^2], mean ± SD	28.6 ± 6.1
Sex [*n (%)*]	
male	267 (59%)
female	182 (41%)
Ethnicity [*n (%)*]	
Caucasian	441 (98%)
other	8 (2%)

Source: Statistical Tables 10 and 15.

Disease-related baseline characteristics of the landiolol user population are shown in Table 4. 73% (328/449) of patients were treated with landiolol for atrial fibrillation, followed by non-compensatory sinus tachycardia affecting 10% (47/449) of patients and atrial flutter affecting 9% (42/449) of patients. The average HR at baseline in the whole study population was 132.4 ± 26.4 bpm. In terms of the medical conditions directly associated with rhythm disorder, the most common were sepsis (42/449 patients, 9%), myocardial infarction (36/449, 8%), surgery (33/449, 7%), and acute decompensated heart failure (30/449, 7%). Tachycardia as a primary reason for treatment was not contemplated in the eCRF, although it was sometimes indicated under “Other”. Nevertheless, the underlying medical condition was only available for approximately one-third of the patients. Moreover, the reason for hospital admission is unknown as it was not queried in the eCRF. The actual numbers of patients with sepsis, myocardial infarction, and heart failure at the start of landiolol treatment, used in the subgroup analysis (following sections), are slightly higher than those reported above. This is because sepsis, myocardial infarction, or heart failure ongoing at the time of treatment initiation were not considered as the medical conditions directly associated with rhythm disorder in some

patients and such patients were then solely included into the respective subgroups (and not among the medical conditions directly associated with rhythm disorder).

The most frequently reported medical histories among patients were arterial hypertension (228 patients, 51%), atrial fibrillation (122, 27%), diabetes mellitus (116, 26%), hyperlipidemia (114, 25%) and coronary heart disease (87, 19%). The information about LV function is available for approximately 38% (171/449) of patients. Of these patients, the majority (107/171) presented already some degree of LV dysfunction, showing LVEF<50% (normal range 50-70% in the healthy population).

Table 4: Disease-related baseline characteristics.

	All patients
N	449
Underlying rhythm disorder (landiolol indication) [n (% total pop)]	449
Other supraventricular tachycardia	6 (1%)
Rapid control of ventricular rate in patients with atrial fibrillation	328 (73%)
Rapid control of ventricular rate in patients with atrial flutter	42 (9%)
For the short-term control of the ventricular rate	11 (2%)
Non-compensatory sinus tachycardia	47 (10%)
Other	14 (3%)
N/A[1]	1 (0.2%)
Condition directly associated with rhythm disorder[2] [*n* (% total pop)]	182 (41%)
Other[3]	60 (13%)
Sepsis	42 (9%)
Myocardial infarction	36 (8%)
Surgery	33 (7%)
Acute decompensated heart failure	30 (7%)
Comorbidities [*n* (% total pop)]	346 (77%)
Arterial hypertension	228 (51%)
Other	187 (42%)
Atrial fibrillation	122 (27%)
Diabetes mellitus	116 (26%)
Hyperlipidemia	114 (25%)
Coronary heart disease	87 (19%)
Chronic heart failure	58 (13%)
Renal failure/Chronic Kidney Disease (CKD)	51 (11%)
Valvular disease	42 (9%)
Chronic Obstructive Pulmonary Disease (COPD)	30 (7%)
LVEF [n (% total pop)]	171 (38%)
Hyperdynamic (>70%)	4 (0.9%)
Normal (50-70%)	60 (13%)
Mild-to-moderate dysfunction (30-49%)	57 (13%)
Severe dysfunction (<30%)	50 (11%)
Heart rate [bpm]	132.4 ± 26.4

For heart rate mean and standard deviation are shown. Source: Statistical Table 11.
[1]For one patient in an Austrian site, the study staff entered usage data but did not specify indication for landiolol.
[2]For some patients, more than one medical condition was reported in the eCRF.

[3]This encompasses the eCRF options "Other" (56 patients), "Thyrotoxicosis" (2 patients), "Catheter ablation therapy" (1 patient), and "Hypertensive crisis" (1 patient).

Regarding the use of other medications, the majority (78%) of patients were concomitantly administered other antiarrhythmics, half (50%) were on antihypertensives and few (12%) were on inotropes (Table 5).

Table 5: Concomitant medication at the start of treatment

	All patients
N	449
Concomitant medication [n (% total pop)]	399 (89%)
Other antiarrhythmics	350 (78%)
Inotropic agents	54 (12%)
Calcium antagonists	64 (14%)
Antihypertensive agents	223 (50%)

Source: Statistical Table 11.

10.4. Landiolol usage

The total dose infused, the duration of infusion (minutes), the minimum dose and the maximum dose, and preferred route of application (central or peripheral line) are presented for the whole population and pre-specified subgroups (Tables 6-9). In total, 449 patients were treated with landiolol, had evaluable data for the primary endpoint evaluation, and were thus included in the analysis. Of these, 20 participants received 2 treatments each and 4 participants received 3 treatments each, totaling 477 treatments overall.

In the whole population, the median landiolol infusion duration was 8.9 hours, ranging from 3 minutes to 20 days. The median duration of landiolol administration in the different hospital settings was 2 h in the ECU and 22 h in the ICU and normal hospital ward (Table 6). Landiolol was administered for a median duration of 7, 4 and 31 h in patients suffering from atrial fibrillation, atrial flutter, and non-compensatory sinus tachycardia, respectively (Table 7). The severe concomitant illnesses prolonged landiolol administration, with the median duration of 20, 15 and 13 h for patients suffering from sepsis, heart failure and myocardial infarction, respectively (Table 8). On contrary, patients without the presence of sepsis, heart failure and myocardial infarction had the median duration of 8, 7 and 9 h, respectively. The patients who were concomitantly administered antiarrhythmic agents had a shorter median duration of landiolol administration (7 h) than the patients without antiarrhythmic agents (17 h) (Table 9). The opposite was observed for the inotropic agents, as the duration of landiolol administration was longer in patients with their concomitant use (27 vs 7 h). Landiolol was administered for 2 and 4 h in patients undergoing concomitant electric cardioversion and cardiac ablation, respectively.

The median starting infusion rate was 5 µg/kg/min, also varying widely among patients (from 0.7 and 100 µg/kg/min). Since data was collected per standard care practice without pre-specified timepoints, it is unclear whether the reported starting dose corresponds to the actual first dose given to all patients, possibly missing information on any bolus injection. The highest starting doses were administered in the ECU with a median dose of 10 µg/kg/min, followed by

the ICU and normal hospital ward with median dose of 4 and 3 µg/kg/min, respectively. Patients with sepsis, heart failure and myocardial infarction were administered lower initial doses than the patients without these concomitant illnesses.

The median lowest and highest dose were 4 and 10 µg/kg/min, respectively. The highest doses of landiolol were administered to the patients in the ECU, with the median lowest and highest doses of 10 and 30 µg/kg/min, respectively. The lowest and highest doses administered to the patients in the ICU (3 and 8 µg/kg/min) and normal hospital ward (2 and 8 µg/kg/min) were comparable. Patients with sepsis, heart failure and myocardial infarction were administered lower doses than the patients without these concomitant illnesses (Table 8). Patients with concomitant use of antiarrhythmic agents were administered higher doses of landiolol than the patients without, while slightly lower doses of landiolol were used in patients with concomitant use of inotropic agents (Table 9). None of the patients received landiolol at a dose higher than that recommended in the SmPC, that is 100 µg/kg/min, and only two patients were given a maximum dose 81-100 µg/kg/min.

All in all, patients received a median total dose of 300 mg, with a minimum of 0.01 over 3 minutes and a maximum of 11,477 mg over 7 days. The subgroup analysis revealed that the highest total dose was administered in the ICU (Table 6, Figure 4, median: 540 mg), for the treatment of non-compensatory sinus tachycardia (Table 7, median: 981 mg), and in association with sepsis (Table 8, median: 498 mg). Conversely, the lowest total dose was administered in the ECU (Table 6, median: 300 mg), for the treatment of atrial flutter (Table 7, median: 300 mg), and in association with myocardial infarction (Table 8, median: 300 mg). A by-patient listing of drug utilization patterns is included in Appendix 13.2 – Primary Endpoint.

Although landiolol was administered equally via central and peripheral lines in the whole population, the central line was the preferred route in intensive care, whereas the peripheral line was favored in emergency care (Table 6). The proportion of central and peripheral lines was similar among all types of arrhythmias, except from non-compensatory sinus tachycardia patients in whom central line was a preferred route of application in 90% (46/477) of cases (Table 7). Central line was more prevalent in patients with sepsis (75% (39/52)) and heart failure (59% (43/73)), while peripheral line was slightly more prevalent in myocardial infarction patients (58% (28/48)) (Table 8). The application via central line was used in most patients using concomitantly inotropic agents (89% (55/62) (Table 9).

Table 6: Landiolol utilization patterns by hospital setting

	All treatments	Hospital setting					
		intensive care unit	emergency care unit	postoperative monitoring care	normal hospital ward	outpatient clinic	other
n[1]	477	250	185	1	39	1	1
Infusion duration [*h*]	8.92 (482.0)	21.63 (481.8)	2.00 (265.95)	14.10	22.00 (233.77)	1.38	25.77
Starting infusion rate [µg/kg/min]	5.26 (99.33)	3.90 (99.33)	10.00 (96.25)	22.00	3.08 (9.00)	10.00	2.50
Lowest infusion rate [µg/kg/min]	4.00 (100.00)	2.50 (100.00)	10.00 (30.00)	10.00	2.14 (9.35)	10.00	0.00

Highest infusion rate [µg/kg/min]	10.00 (98.57)	8.10 (98.57)	30.00 (96.00)	22.00	7.87 (78.35)	80.00	2.50
Total dose infused [mg]	300.00 (11476.79)	540.40 (11474.71)	300.00 (7850.99)	1602.00	440.00 (6257.65)	300.00	309.07
Route of application [*n*, %]							
Central line	253 (53%)	188 (75%)	43 (23%)	0	21 (54%)	0	1
Peripheral line	215 (45%)	56 (22%)	142 (77%)	1	15 (38%)	1	0
Reason for discontinuation [*n*, %]							
Treatment effective	321 (67%)	200 (80%)	89 (48%)	1	30 (77%)	1	0
Adverse event	9 (2%)	4 (2%)	2 (1%)	0	3 (8%)	0	0
Other[2]	142 (30%)	44 (18%)	91 (49%)	0	6 (15%)	0	1
Heart rate at start of infusion [bpm]	132.27 (26.64)	128.57 (26.22)	139.16 (25.35)	164.00 (0.00)	122.71 (28.76)	117.00 (0.00)	119.00 (0.00)
Heart rate at end of infusion [bpm]	103.00 (24.50)	98.19 (24.22)	111.42 (22.93)	140.00 (0.00)	94.58 (21.69)	71.00 (0.00)	73.00 (0.00)

For all drug utilization parameters median and range are shown. For heart rate mean and standard deviation are presented instead. [1]These are number of landiolol treatments, not number of patients. [2]Under the category "Other", "death", "died" or "exitus letalis" was reported for 10 patients.
Source: Statistical Tables 38 and 41.

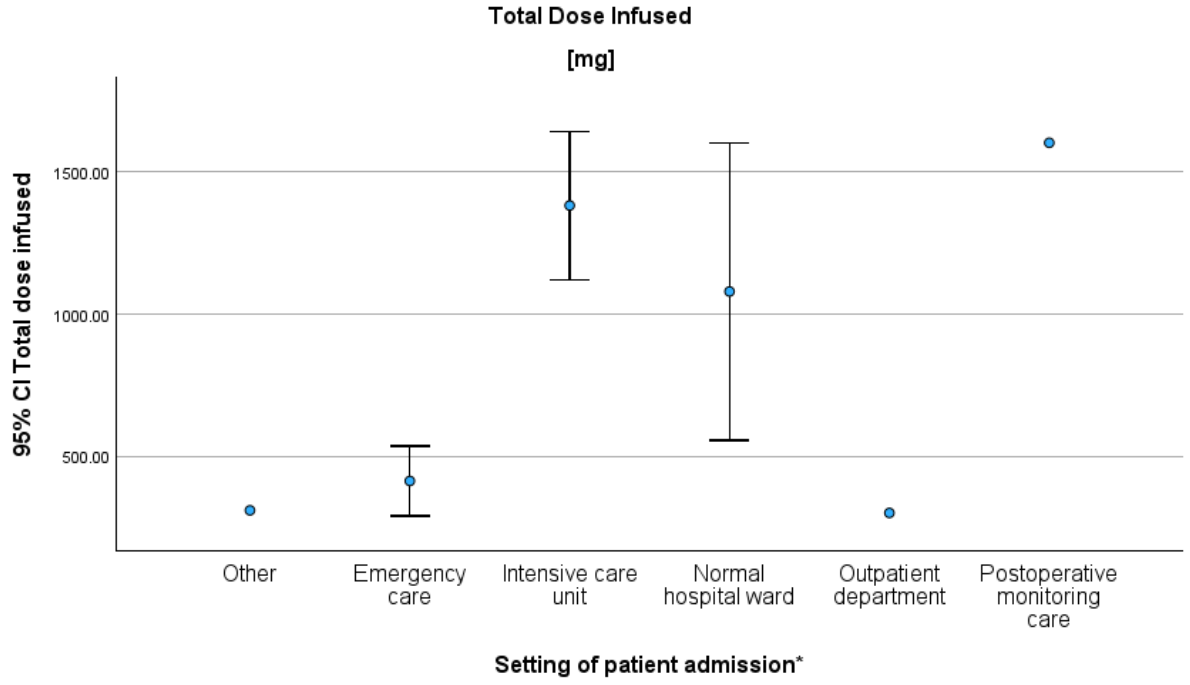

Figure 4: Landiolol usage and hospital setting. Mean and 95% confidence intervals. Source: Statistical Figure 25.

The treatment with landiolol was considered effective and discontinued in 67% (321/477) cases. This result was driven by the patients in the ICU and normal hospital ward, with 80% (200/250) and 77% (30/39) effectiveness of the treatment. The treatment was effective and thus discontinued in 48% (89/185) patients in the ECU. The discontinuation of landiolol due to

treatment efficacy was mostly prevalent in patients with myocardial infarction (88% (42/48)) and sepsis (77% (40/52)). This result is also supported by a reduction in HR upon treatment, as the mean (± SD) HR was 132 ± 27 and 103 ± 25 bpm before and after infusion, respectively. Treatment success is analyzed in greater detail at V3 in section 10.5, offering a more objective measure of treatment efficacy. The treatment was discontinued due to AEs in 2% (9/477) of the treatment sessions. In the "Other" category (142/477), there were 109 cases of treatment either ineffective or only mildly effective and 10 cases of death (not treatment-related).

Table 7: Landiolol utilization patterns by indication

	Type of arrhythmia						
	Rapid control of ventricular rate in patients with atrial fibrillation	Non-compensatory sinus tachycardia	Rapid control of ventricular rate in patients with atrial flutter	other	Short-term control of the ventricular rate	Other supraventricular tachycardia	not applicable
n[1]	351	51	42	15	11	6	1
Infusion duration [*h*]	7.00 (234.95)	31.00 (481.35)	4.17 (352.77)	36.68 (265.15)	27.00 (295.63)	11.88 (186.80)	130.27 (-)
Highest infusion rate [µg/kg/min]	11.32 (98.57)	6.70 (37.73)	18.77 (95.60)	8.20 (55.71)	5.00 (11.70)	10.33 (78.35)	24.44 (-)
Total dose infused [mg]	300.00 (7559.99)	980.55 (11185.56)	300.00 (5588.00)	626.40 (7836.07)	516.00 (11449.92)	300.00 (6291.60)	6606.71 (-)
Route of application [n, %]							
Central line	173 (49%)	46 (90%)	15 (36%)	9 (60%)	5 (45%)	4 (67%)	1 (-)
Peripheral line	172 (49%)	3 (6%)	26 (62%)	6 (40%)	6 (55%)	2 (33%)	0 -
Heart rate at start of infusion [bpm]	134.80 (26.13)	122.37 (20.50)	128.86 (23.59)	114.86 (28.52)	126.10 (47.42)	139.17 (43.93)	-
Heart rate at end of infusion [bpm]	104.68 (24.79)	92.08 (15.69)	108.79 (26.03)	87.80 (20.85)	102.73 (30.46)	100.50 (22.29)	-

For all drug utilization parameters median and range are shown. For heart rate mean and standard deviation are presented instead.
[1]Number of landiolol treatments, not number of patients. Source: Statistical Table 37.

Table 8: Landiolol utilization patterns by medical condition of interest

	Sepsis at the start of treatment		Heart failure at the start of treatment		Myocardial infarction at the start of treatment	
	Yes	No	Yes	No	Yes	No
n[1]	52	425	73	404	48	429
Infusion duration [*h*]	20.00 (227.92)	7.75 (481.95)	14.50 (333.83)	7.00 (481.95)	13.02 (231.20)	8.50 (481.78)
Highest infusion rate [µg/kg/min]	6.65 (98.00)	11.31 (96.20)	8.70 (98.00)	10.90 (96.17)	6.41 (78.00)	10.95 (98.57)
Total dose infused [mg]	498.00 (11178.98)	300.00 (11476.79)	302.08 (11441.52)	300.00 (11189.99)	300.00 (7079.99)	300.00 (11474.71)
Route of application [n, %]						
Central line	39 (75%)	214 (50%)	43 (59%)	210 (52%)	20 (42%)	233 (54%)
Peripheral line	9 (17%)	206 (48%)	29 (40%)	186 (46%)	28 (58%)	187 (44%)

Heart rate at start of infusion [bpm]	129.08 (27.22)	132.66 (26.58)	126.99 (25.41)	132.27 (26.64)	119.25 (22.26)	133.73 (26.72)
Heart rate at end of infusion [bpm]	105.50 (24.87)	102.70 (24.46)	109.11 (26.88)	103.00 (24.50)	100.00 (26.01)	103.34 (24.33)

For all drug utilization parameters median and range are shown. For heart rate mean and standard deviation are presented instead.
[1]Number of landiolol treatments, not number of patients. Source: Statistical Table 39.

Table 9: Landiolol utilization patterns by concomitant treatments

	Antiarrhythmic agents		Inotropic agents		Electric cardioversion		Cardiac ablation	
	Yes	No	Yes	No	Yes	No	Yes	No
n[1]	374	103	62	415	27	450	5	472
Infusion duration [*h*]	7.27 (481.95)	17.00 (353.20)	27.05 (334.78)	7.00 (481.95)	1.75 (187.35)	8.92 (481.95)	4.37 (297.82)	9.00 (481.95)
Highest infusion rate [µg/kg/min]	12.00 (98.00)	7.78 (78.57)	8.00 (78.00)	10.65 (98.57)	20.00 (95.60)	10.00 (98.57)	5.90 (77.50)	10.00 (98.57)
Total dose infused [mg]	300.00 (11476.79)	302.08 (7848.91)	987.57 (7593.91)	300.00 (11476.79)	300.00 (6294.67)	300.00 (11476.79)	300.00 (10752.91)	300.00 (11476.79)
Route of application [*n*, *%*]								
Central line	175 (47%)	78 (76%)	55 (89%)	198 (48%)	4 (15%)	249 (55%)	2 (40%)	251 (53%)
Peripheral line	190 (51%)	25 (24%)	5 (8%)	210 (51%)	23 (85%)	192 (43%)	3 (60%)	212 (45%)
Heart rate at start of infusion [bpm]	135.28 (26.30)	121.42 (25.10)	130.26 (30.34)	132.57 (26.07)	131.19 (22.31)	132.33 (26.90)	140.00 (50.56)	132.27 (26.64)
Heart rate at end of infusion [bpm]	104.63 (24.90)	97.13 (22.11)	104.53 (26.46)	102.77 (24.21)	109.81 (32.67)	102.59 (23.90)	102.20 (7.53)	103.00 (24.50)

For all drug utilization parameters median and range are shown. For heart rate mean and standard deviation are presented instead.
[1]Number of landiolol treatments, not number of patients. Source: Statistical Table 40.

10.5. Efficacy results

Effectiveness of landiolol treatment was assessed within 4 hours after landiolol discontinuation (at V3) based on:

- Percentage of patients with a HR control (heart rate ≤ 110 bpm or 20% less than baseline [immediately before landiolol treatment])
- Percentage of patients who recover the normal sinus rhythm
- Percentage of patients with a HR control ≤ 90 bpm
- Proportion of patients requiring additional pharmacological or electrical cardioversion for rhythm control during hospital stay

About 75% (333/449) of patients achieved a HR ≤110 bpm or >20% reduction within 4h after landiolol treatment discontinuation when compared to the baseline. The HR control ≤110 bpm was achieved in 89% [42/49], 73% [240/328] and 69% [29/42] of patients suffering from non-compensatory sinus tachycardia, atrial fibrillation and atrial flutter, respectively, and in 83% [189/229], 65% [117/179] and 66% [25/38] of patients treated in the ICU, ECU, and normal

hospital ward, respectively. Furthermore, 50% (224/449) of patients achieved a HR ≤90 bpm within 4h after landiolol treatment discontinuation. The HR ≤90 bpm was achieved in 68% [32/47], 46% [152/328] and 50% [21/42] of patients suffering from non-compensatory sinus tachycardia, atrial fibrillation and atrial flutter, respectively, and in 61% [139/229], 35% [63/179], and 55% [21/38], of patients treated in the ICU, ECU, and normal hospital ward, respectively. Overall, the highest proportion of patients with HR control was observed in the ICU (Table 10), for non-compensatory sinus tachycardia (Table 11), for those with myocardial infarction (Table 12), and for those on inotropic agents (Table 13).

Table 10: Effectiveness of landiolol treatment at V3 by hospital setting

	All patients	Hospital setting					
		intensive care unit	emergency care unit	postoperative monitoring care	normal hospital ward	outpatient clinic	other
N	449	229	179	1	38	1	1
Patients with [*n, %*]:							
Heart rate ≤110 bpm or <20% baseline	333 (74%)	189 (83%)	117 (65%)	1	25 (66%)	0	0
Heart rate ≤90 bpm	224 (50%)	139 (61%)	63 (35%)	1	21 (55%)	0	0
Recovery of normal sinus rhythm	187 (42%)	119 (52%)	54 (30%)	1	12 (32%)	0	1
Patients requiring additional therapy for rhythm control [*n, %*]	190 (42%)	60 (26%)	118 (66%)	0	11 (29%)	1	0
Use of concomitant medication [*n, %*]	399 (89%)	185 (81%)	178 (99%)	1	33 (87%)	1	1
Time to heart rate control (min)[1] [median (range)[2]]	181 (257621)	195 (212387)	180 (257619)	161 (257621)	195 (254708)	180 (179770)	186 (257621)

[1]Time to reach heart rate ≤110 bpm, calculated as start date/time of obtaining heart rate control – end date of landiolol treatment.
[2]Range = max-min
Source: Statistical Table 97.

With regard to recovery of normal sinus rhythm, 42% (187/449) of patients did recover normal sinus rhythm within 4h after landiolol treatment discontinuation. The highest recovery rate (81% (38/47)) was observed in non-compensatory sinus tachycardia patients; however, this is also the condition mostly characterized by normal sinus rhythm. Among patients with tachyarrhythmias, the percentage of patients who recovered the normal sinus rhythm was 37% (122/328) and 33% (14/42) for those with atrial fibrillation and atrial flutter, respectively (Table 11). It is worth noting that these results include a substantial number of patients who died during safety observation period V2-V5 (25%, see Figure 3) who were covered by a waiver. Thus, this efficacy analysis is not likely to be skewed to higher success rates by patients dropping out of the study.

Table 11: Effectiveness of landiolol treatment at V3 by indication

	Type of arrhythmia						
	patients with atrial fibrillation	Non-compensatory sinus tachycardia	patients with atrial flutter	other	Short-term control of the ventricular rate	Other supraventricular tachycardia	not applicable
N	328	47	42	14	11	6	1
Patients with [*n, %*]:							
Heart rate ≤110 bpm or <20% from baseline	240 (73%)	42 (89%)	29 (69%)	8 (57%)	7 (64%)	6 (100%)	1
Heart rate ≤90 bpm	152 (46%)	32 (68%)	21 (50%)	6 (43%)	7 (64%)	5 (83%)	1
Recovery of normal sinus rhythm	122 (37%)	38 (81%)	14 (33%)	2 (14%)	7 (64%)	3 (50%)	1
Patients requiring additional therapy for rhythm control [*n, %*]	154 (47%)	4 (9%)	23 (55%)	5 (36%)	1 (9%)	2 (33%)	1
Use of concomitant medication [*n, %*]	302 (92%)	31 (66%)	38 (90%)	14 (100%)	9 (82%)	4 (67%)	1
Time to heart rate control ≤110 bpm (min)[1] [median (range)[2]]	204 (257621)	180 (10073)	150 (140658)	140 (107900)	149 (159)	180 (10073)	-

[1]Time to reach heart rate ≤110 bpm, calculated as start date/time of obtaining heart rate control – end date of landiolol treatment.
[2]Range = max-min
Source: Statistical Table 96.

A total of 42% (190/449) of patients required additional pharmacological or electrical cardioversion for rhythm control (Table 10). Of these, 86 patients showed HR control ≤90 bpm, but only 53 showed both HR control ≤90 bpm and sinus rhythm recovery. The pharmacological treatments for rhythm control included the following medications: flecainide, propafenone, amiodarone, dronedarone, and sotalol. By-subject listings of all efficacy endpoints are provided in Appendix 13.2 – Secondary endpoints. The majority of patients (89% (399/449)) used concomitant medication during the treatment with landiolol.

Table 12: Effectiveness of landiolol treatment at V3 by medical condition of interest

	Sepsis at the start of treatment		Heart failure at the start of treatment		Myocardial infarction at the start of treatment	
	Yes	No	Yes	No	Yes	No
N	44	405	69	380	41	408
Patients with [*n, %*]:						
Heart rate ≤110 bpm or <20% baseline	34 (77%)	299 (74%)	47 (68%)	286 (75%)	34 (83%)	299 (73%)
Heart rate ≤90 bpm	23 (52%)	201 (50%)	25 (36%)	199 (52%)	25 (61%)	199 (49%)

Recovery of normal sinus rhythm	26 (59%)	121 (30%)	26 (38%)	161 (42%)	26 (63%)	161 (39%)
Patients requiring additional therapy for rhythm control [*n, %*]	10 (23%)	180 (44%)	22 (32%)	168 (44%)	7 (17%)	183 (45%)
Use of concomitant medication [*n, %*]	35 (80%)	364 (90%)	67 (97%)	332 (87%)	40 (98%)	359 (88%)
Time to heart rate control ≤110 bpm (min)[1] [median (range)][2]	182 (257621)	180 (212383)	190 (175803)	180 (257620)	155 (8444)	190 (257621)

[1]Time to reach heart rate ≤110 bpm, calculated as start date/time of obtaining heart rate control – end date of landiolol treatment.
[2]Range = max-min
Source: Statistical Table 98.

Table 13: Effectiveness of landiolol treatment at V3 by concomitant treatments

	Antiarrhythmic agents		Inotropic agents		Electric cardioversion		Cardiac ablation	
	Yes	No	Yes	No	Yes	No	Yes	No
N	350	99	54	395	27	422	4	445
Patients with [*n, %*]:								
Heart rate ≤110 bpm or <20% baseline	256 (73%)	77 (78%)	43 (80%)	290 (73%)	20 (74%)	313 (74%)	2 (50%)	331 (74%)
Heart rate ≤90 bpm	164 (47%)	60 (61%)	28 (52%)	196 (50%)	13 (48%)	211 (50%)	1 (25%)	223 (50%)
Recovery of normal sinus rhythm	134 (38%)	53 (54%)	30 (56%)	157 (40%)	9 (33%)	178 (42%)	0	187 (42%)
Patients requiring additional therapy for rhythm control [*n, %*]	169 (48%)	21 (21%)	20 (37%)	170 (43%)	20 (74%)	170 (40%)	2 (50%)	188 (42%)
Use of concomitant medication [*n, %*]	350 (100%)	49 (49%)	54 (100%)	345 (87%)	27 (100%)	372 (88%)	4 (100%)	395 (89%)
Time to heart rate control ≤110 bpm (min)[1] [median (range)][2]	182 (257621)	180 (212383)	190 (175803)	180 (257620)	155 (8444)	190 (257621)	720 (16951)	182 (257621)

[1]Time to reach heart rate ≤110 bpm, calculated as start date/time of obtaining heart rate control – end date of landiolol treatment.
[2]Range = max-min
Source: Statistical Table 99.

10.6. Safety results

Safety of landiolol treatment was assessed up to 180 days after landiolol initiation based on:

- AEs concerning number of patients and events, incidence rate, seriousness, intensity and relationship to study drug
- AEs requiring discontinuation of the treatment
- AEs requiring treatment with specific therapy
- Length of ICU/ ECU/ hospital stay
- MACE incidence broken down by type: transient ischemic attack or ischemic stroke, myocardial infarction (STEMI and NSTEMI), cardiovascular death, all-cause mortality, unstable angina, hospitalization for heart failure, de-novo atrial fibrillation requiring specific treatment.

A summary of all AEs recorded in the study is presented in Table 14. In total, 123 AEs were reported in 79 patients (18% of the study population). Of these AEs, 56 were considered serious AEs (SAEs). None of the AEs was assessed to be related to the landiolol treatment. A total of 6 AEs in 6 patients led to the permanent discontinuation of the landiolol treatment (1%). These included 4 instances of hypotension (patients AT-G01-00028, AT-G01-00024, GR-A01-00017, and GR-A02-00001), 1 instance of mixed cardiogenic-septic shock (patient AT-G01-00020), and 1 instance of severe hypotension due to hemorrhagic shock (patient GR-A01-00018). A by-patient listing of all AEs is provided in Appendix 13.2 – Adverse events.

Table 14: Summary of adverse events

			Hospital Setting					
	All patients *N* =449		intensive care unit *N* = 229		emergency care unit *N* = 179		other settings[1] *N* = 41	
	nE	nS	nE	nS	nE	nS	nE	nS
Any AE	123	79 (18%)	36	27 (12%)	72	41 (23%)	15	11 (26%)
AE leading to discontinuation of the treatment[2]	6	6 (1%)	4	4 (2%)	1	1 (1%)	1	1 (3%)
AE seriousness								
Yes	56	36 (8%)	24	15 (7%)	23	14 (8%)	9	7 (18%)
No	53	40 (9%)	12	12 (5%)	35	32 (18%)	6	6 (13%)
AE intensity								
Mild	14	14 (3%)	7	7 (3%)	5	5 (3%)	2	2 (5%)
Moderate	15	13 (3%)	8	6 (3%)	4	4 (2%)	3	3 (8%)
Severe	47	33 (7%)	21	14 (6%)	18	12 (7%)	8	7 (18%)
AE relationship to landiolol								
Possible/Probable/Certain	0	0	0	0	0	0	0	0
Unrelated/Unlikely	73	52 (12%)	36	27 (12%)	23	15 (8%)	14	10 (26%)

nE, number of events; *nS*, number of subjects. Source: Statistical Table 187.
[1]Other settings include normal hospital ward (38 patients), postoperative monitoring care (1), outpatient clinic (1) and other (1).
[2]This refers to the field "Landiolol permanently discontinued".

Table 15 shows the AEs recorded in this study according to MedDRA system organ classes (SOC) and preferred terms (PT). Most AEs were classified under the SOC cardiac disorders (72 events in 49 patients), followed by respiratory, thoracic and mediastinal disorders (12 events in 12 patients) and vascular disorders (11 events in 11 patients). The most frequently reported PTs were atrial fibrillation (33 events in 24 patients), hypotension (9 events in 9 patients), cardiac arrest (7 events in 6 patients), atrial flutter (6 events in 5 cases), and multiple organ dysfunction syndrome and cardiac failure (5 events in 5 patients each). Bradycardia was reported in 1 patient.

Table 15: Adverse events by system organ class and preferred term

Any event			Hospital Setting					
	All patients *N* =449		intensive care unit *N* = 229		emergency care unit *N* = 179		other settings[1] *N* = 41	
	nE	nS	nE	nS	nE	nS	nE	nS
Blood and lymphatic system disorders	**2**	**2**	**1**	**1**	**1**	**1**	**0**	**0**
Anemia	1	1	0	0	1	1	0	0
Blood loss anemia	1	1	1	1	0	0	0	0
Cardiac disorders	**72**	**49**	**45**	**30**	**18**	**11**	**9**	**8**
Angina pectoris	1	1	1	1	0	0	0	
Atrial fibrillation	33	24	29	20	2	2	2	2
Atrial flutter	6	5	5	4	0	0	1	1
Atrioventricular block second degree	1	1	1	1	0	0	0	0
Bradycardia	1	1	0	0	1	1	0	0
Cardiac arrest	7	6	1	1	4	3	2	2
Cardiac disorder	1	1	1	1	0	0	0	0
Cardiac failure	5	5	1	1	2	2	2	2
Cardiac tamponade	1	1	1	1	0	0	0	0
Cardiogenic shock	3	3	1	1	1	1	1	1
Low cardiac output syndrome	2	1	0	0	2	1	0	0
Pericardial effusion	1	1	1	1	0	0	0	0
Pericardial hemorrhage	1	1	1	1	0	0	0	0
Sinus arrest	1	1	0	0	1	1	0	0
Supraventricular tachycardia	1	1	1	1	0	0	0	0
Torsade de pointes	2	1	0	0	2	1	0	0
Ventricular fibrillation	3	3	1	1	2	2	0	0
Ventricular tachycardia	2	2	0	0	1	1	1	1
Ear and labyrinth disorders	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
Deafness	1	1	1	1	0	0	0	0
Eye disorders	**1**	**1**	**0**	**0**	**1**	**1**	**0**	**0**
Corneal erosion	1	1	0	0	1	1	0	0
Gastrointestinal disorders	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
Upper gastrointestinal hemorrhage	1	1	1	1	0	0	0	0
General disorders and administration site conditions	**7**	**7**	**4**	**4**	**2**	**2**	**1**	**1**
Chest pain	2	2	2	2	0	0	0	0
Multiple organ dysfunction syndrome	5	5	2	2	2	2	1	1
Infections and infestations	**7**	**7**	**4**	**4**	**2**	**2**	**1**	**1**
Pneumonia	2	2	1	1	0	0	1	1
Sepsis	2	2	2	2	0	0	0	0
Septic shock	3	3	1	1	2	2	0	0

Investigations	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
C-reactive protein increased	1	1	1	1	0	0	0	0
Metabolism and nutrition disorders	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
Hypokalemia	1	1	1	1	0	0	0	0
Metabolism and nutrition disorders (or Blood Disorder)	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
Hyponatremia	1	1	1	1	0	0	0	0
Nervous system disorders	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
Hypotonic-hyporesponsive episode	1	1	1	1	0	0	0	0
Product issues	1	1	0	0	1	1	0	0
Lead dislodgement	1	1	0	0	1	1	0	0
Renal and urinary disorders	3	3	1	1	1	1	1	1
Acute kidney injury	2	2	1	1	1	1	0	0
Renal failure	1	1	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	12	12	9	9	2	2	1	1
Acute respiratory distress syndrome	1	1	1	1	0	0	0	0
Asthma	1	1	1	1	0	0	0	0
Dyspnea	3	3	3	3	0	0	0	0
Interstitial lung disease	1	1	1	1	0	0	0	0
Pleural effusion	3	3	2	2	1	1	0	0
Respiratory failure	3	3	1	1	1	1	1	1
Skin and subcutaneous tissue disorders	1	1	1	1	0	0	0	0
Alopecia	1	1	1	1	0	0	0	0
Vascular disorders	11	11	1	1	8	8	2	2
Hypertension	1	1	0	0	1	1	0	0
Hypotension	9	9	1	1	6	6	2	2
Shock	1	1	0	0	1	1	0	0

nE, number of events; *nS*, number of subjects. Source: Statistical Tables 191 and 196, and Appendix I to the statistical report.
[1]Other settings include normal hospital ward (38 patients), postoperative monitoring care (1), outpatient clinic (1) and other (1).

A total of 113 MACEs were reported in 112 patients, affecting 25% of the study population (Table 16). The discrepancies between the numbers in Tables 14 and 16 arise because the AE box was not consistently checked when reporting a new MACE. Within 6 months of landiolol treatment, 25% (110/499) of patients had died. Of these, 36% (40/110) of patients died due to cardiovascular death. For the remaining 64% (70/110) of patients, other causes of death were reported. The highest death rates were recorded for the patients who were treated in the ICU at time of the tachycardia onset (35%, 80/229), for the indication of non-compensatory sinus tachycardia (43%, 20/47), for patients with sepsis at start of treatment (57%, 25/44), or on inotropes (60%, 32/54) (Statistical Tables 155-158). One patient suffered from an ischemic stroke and another two patients experienced de-novo atrial fibrillation. None of the 113 MACEs was assessed to be related to the landiolol treatment. A by-patient listing of all MACEs is shown in Appendix 13.2 – MACEs.

Table 16: Major adverse cardiac events

			Hospital setting					
	All patients *N* =449		intensive care unit *N* = 229		emergency care unit *N* = 179		other settings[2] *N* = 41	
	nE	*nS*	nE	*nS*	nE	*nS*	nE	*nS*
Any MACE	113	112	83	82	17	17	13	13
All-cause mortality[1]	110	110 (25%)	80	80 (35%)	17	17 (10%)	13	13 (32%)
Transient ischemic attack or ischemic stroke	1	1 (0.2%)	1	1 (0.4%)	0	0	0	0
Myocardial infarction (STEMI and NSTEMI)	0	0	0	0	0	0	0	0
Unstable angina	0	0	0	0	0	0	0	0
Hospitalization for heart failure	0	0	0	0	0	0	0	0
De-novo atrial fibrillation requiring specific treatment	2	2 (0.5%)	2	2 (0.9%)	0	0	0	0
Cardiovascular death	40	40 (9%)	28	28 (12%)	5	5 (3%)	7	7 (16%)
Death NOS	70	70 (16%)	52	52 (23%)	12	12 (7%)	6	6 (16%)

nE, number of events; *nS*, number of subjects; NOS, not otherwise specified. Source: Statistical Table 156.
[1]A total of 11 death events, which have not been recorded as MACE in the eCRF, have been imputed: patients AT-W01-00011 and PL-L01-00003 (cardiovascular death), patients AT-L01-00008, AT-L01-00013, AT-W01-00008, AT-W01-00012, GR-A02-00003, GR-N01-00003, GR-N01-00006, PL-L01-00004 and PL-L01-00005 (death NOS).
[2]Other settings include normal hospital ward (38 patients), postoperative monitoring care (1), outpatient clinic (1) and other (1).

A total of 33 patients (7% of the whole user population) required treatment with specific therapy to resolve 52 AEs (Table 17). This percentage was higher in the ICU, where 7 patients (31% of the user population in this setting) required specific therapy.

Table 17: AEs requiring treatment with specific therapy

			Hospital Setting					
	All patients *N* =449		intensive care unit *N* = 229		emergency care unit *N* = 179		other settings[1] *N* = 41	
	nE	nS	nE	nS	nE	nS	nE	nS
Any AE	123	79	36	27	72	41	15	11
AEs requiring specific therapy	52	33 (7%)	11	7 (31%)	36	22 (12%)	5	4 (10%)

nE, number of events; *nS*, number of subjects. Source: Statistical Table 201.
[1]Other settings include normal hospital ward (38 patients), postoperative monitoring care (1), outpatient clinic (1) and other (1).

A by-patient listing of all AEs requiring treatment with specific therapy is shown in Table 18. Electrical cardioversion was employed in 21 patients to restore a regular heart rhythm, primarily in atrial fibrillation, but also in atrial flutter, supraventricular tachycardia and cardiogenic shock. Cardiopulmonary resuscitation was performed in 5 patients associated with ventricular

fibrillation, ventricular tachycardia, cardiogenic shock, or cardiac arrest. Cardiac ablation was used in 3 patients suffering from atrial fibrillation or atrial flutter.

Table 18: AEs requiring specific therapy by PT and intervention

Participant ID	PT term	Specific therapy
AT-G01-00001	Ventricular fibrillation	short CPR was done
AT-G01-00010	Atrial fibrillation	electrical cardioversion
AT-G01-00013	Atrial flutter	dose increase of Landiolol, pacemaker adaptation
AT-G01-00020	Cardiogenic shock	electric and medicinal attempts, retreatment with Landiolol
AT-G01-00020	Cardiac arrest	electric shock via defibrillator
AT-G01-00021	Cardiac failure	increased landiolol for control of the tachycardia, high flow inotropes
AT-G01-00022	Cardiogenic shock	electrical cardioversion
AT-G01-00022	Atrial fibrillation	even with high flow Catecholamines no control possible
AT-G01-00023	Lead dislodgement	sonde revision with change of the pacemaker
AT-W01-00027	Ventricular tachycardia	CPR
AT-W01-00027	Ventricular fibrillation	CPR
AT-W01-00048	Cardiac arrest	CPR
AT-W01-00048	Pneumonia	antibiotics
AT-W11-00003	Cardiogenic shock	CPR
CZ-P02-00006	Acute kidney injury	mineralocorticoid antagonist (Verospiron) terminated, dosage of furosemide reduced + conservative treatment of hyperkalemia and renal failure - hydration, glucose + insulin administration
CZ-P02-00013	Respiratory failure	intubation and mechanical ventilation
CZ-P02-00013	Septic shock	conservative treatment - fluid administration + hemodynamic and ventilatory stabilization effective with gradual restoration of renal function without the need of CRRT
CZ-P02-00013	Multiple organ dysfunction syndrome	conservative treatment - fluid administration + hemodynamic and ventilatory stabilization effective with gradual restoration of renal function without the need of CRRT
DE-D01-00001	Atrial fibrillation	pulmonary vein isolation
DE-D01-00003	Atrial fibrillation	pulmonary vein isolation
DE-D01-00006	Atrial fibrillation	electrical cardioversion
DE-D01-00006	Atrial fibrillation	electrical cardioversion
DE-D01-00009	Atrial fibrillation	electrical cardioversion

Participant ID	PT term	Specific therapy
DE-D01-00009	Atrial fibrillation	electrical cardioversion
DE-D01-00009	Atrial fibrillation	electrical cardioversion
DE-D01-00009	Atrial fibrillation	cryoablation
DE-D01-00010	Atrial fibrillation	(EPU), isolation of the left atrium
DE-D01-00010	Hyponatremia	clip- and endoclot supply glandular cysts in the stomach
DE-D01-00010	Hypokalemia	clip- and endoclot supply glandular cysts in the stomach
DE-D01-00010	Blood loss anemia	clip- and endoclot supply glandular cysts in the stomach
DE-D01-00010	Upper gastrointestinal hemorrhage	clip supply
DE-D01-00012	Atrial fibrillation	electrical cardioversion
DE-D01-00012	Atrial fibrillation	electrical cardioversion
DE-D01-00019	Atrial fibrillation	electrophysiological examination and ablation
DE-D01-00022	Atrial fibrillation	electrical cardioversion
DE-D01-00022	Atrial fibrillation	electrical cardioversion
DE-D01-00022	Atrial fibrillation	electrical cardioversion
DE-D01-00027	Atrioventricular block second degree	temporary pacemaker implantation
DE-D01-00030	Cardiac tamponade	resuscitation, cardiac catheter
DE-D01-00031	Atrial fibrillation	implantation Medtronic Reveal Linq
DE-D01-00034	Atrial fibrillation	electrical cardioversion
DE-D01-00040	Atrial fibrillation	electrical cardioversion
DE-D01-00040	Atrial fibrillation	electrical cardioversion, after cardioversion sinus rhythm
DE-D01-00042	Atrial fibrillation	electrical cardioversion
DE-D01-00042	Supraventricular tachycardia	electrical cardioversion
DE-D01-00044	Atrial flutter	electrical cardioversion
DE-D01-00046	Atrial flutter	circumferential pulmonary vein isolation and left arterial substrate modification- Ablation of a roof dependent atrial flutter
DE-D01-00048	Atrial flutter	electrical cardioversion
DE-D01-00050	Atrial fibrillation	electrical cardioversion (twice)
DE-D01-00051	Atrial fibrillation	electrical cardioversion (twice)
PL-W01-00004	Anemia	Intravenous fluids and blood transfusion. Heparin dose decreased

Participant ID	PT term	Specific therapy
SI-L01-00006	Sepsis	New combination of antibiotics, fluids, oxygen treatment and vasopressor

Source: Statistical Table 205.

Overall, the mean (± SD) length of stay in the ICU, ECU and hospital for the patients who survived and spent at least one day in the ICU or ECU, was 17.3 ± 21.3, 4.6 ± 6.1 and 14.3 ± 18.5 days, respectively (Table 19). The patients who stayed the longest in the hospital were those with non-compensatory sinus tachycardia (33.7 ± 31.6 days), with sepsis at start of treatment (36.0 ± 31.2 days), or on inotropes (26.7 ± 21.5 days) (Statistical Tables 96-99).

Table 19: Length of stay at the hospital (V1-V4)

	All patients	Hospital setting					
		intensive care unit	emergency care unit	postoperative monitoring care	normal hospital ward	outpatient clinic	other
N	449	229	179	1	38	1	1
Length of stay in intensive care (survivors) (days)	17.3 (21.3)	18.2 (21.8)	9.9 (18.1)	0	23.2 (19.3)	0 (-)	0
Length of stay in emergency care (survivors) (days)	4.6 (6.1)	1.8 (1.5)	4.7 (6.2)	-	1 (-)	1 (-)	-
Length of stay in hospital (survivors) (days)	14.3 (18.5)	21.0 (21.8)	7.6 (11.3)	7 (-)	18.4 (19.3)	1 (-)	0

Mean and standard deviation are shown. Source: Statistical Table 97.

Vital signs measured were pulse rate, blood pressure, and blood oxygen saturation. Table 20 shows the mean values of vital signs at each time of assessment. None of them reveal any relevant trends, in particular ones that might indicate an adverse effect of the study treatment.

Table 20: Vital signs for all patients (V1-V5)

	Heart rate (bpm)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Blood oxygen saturation (%)
Visit 1	133 (174)	120 (179)	72 (94)	97 (25)
Visit 2	100 (146)	117 (129)	68 (86)	97 (16)
Visit 3	90 (157)	120 (152)	67 (84)	97 (30)
Visit 4	82 (156)	123 (156)	70 (84)	97 (44)
Visit 5	75 (135)	130 (153)	80 (94)	98 (10)

Median and range are shown. Source: Statistical Tables 210-214.

11. Discussion and Overall Conclusions

In this observational study, we collected real-world data to monitor landiolol utilization patterns, patient characteristics, effectiveness and safety data across 8 European countries. To standardize trial methodology across study sites and minimize variability in study data, we performed training sessions, investigator meetings, and on-site and remote data monitoring sessions. Additional information was circulated via regular newsletters (quarterly, or upon particular milestones).

A total of 450 patients entered the study after being deemed suitable for treatment with intravenous landiolol for their underlying condition by their treating physicians. The waiver allowed data collection for those patients incapable of consenting during hospitalization, which covered approximately 35% of the study population, effectively reducing the threat of selection bias. The follow-up rate for the whole user population was 76% at Visit 4 (hospital discharge) and 55% at Visit 5 (up to 6 months). These numbers are within an expected range considering that intravenous landiolol is primarily used to manage tachycardias in critical care units (Walkey et al., 2011; Kotecha et al., 2014; Obayashi et al., 2021).

11.1. Discussion

This was primarily a drug utilization study to describe the use of landiolol in everyday medical practice, understand the characteristics of the user population, and examine the relationship between recommended and actual clinical practice. The vast majority of patients (90%) received intravenous landiolol either in the intensive or emergency care setting. Approximately three-quarters of patients were indicated landiolol for ventricular rate control in atrial fibrillation, approximately one-tenth for ventricular rate control in atrial flutter, and another one-tenth for non-compensatory sinus tachycardia. Representative of the medical conditions that often trigger arrhythmia in critical care units (Boriani et al., 2019), the most frequent conditions directly associated with rhythm disorder were: sepsis (9%), myocardial infarction (8%), surgery (7%), and acute decompensated heart failure (7%). These incidence rates probably underestimate the real numbers because this information was only available for approximately 40% of patients. The number of patients with sepsis, myocardial infarction, or heart failure at the start of landiolol treatment, who were included into the subgroup analyses, was slightly higher compared to the number of patients presented above. This could be caused by the fact that sepsis, myocardial infarction, or heart failure were not considered as the medical conditions directly associated with rhythm disorder in some patients and such patients were solely included into the respective subgroups.

Patients included in this study often suffered from comorbidities, with arterial hypertension being reported for 51%, atrial fibrillation for 27%, diabetes mellitus for 26% and hyperlipidemia for 25% of the participants. Data on LV function was available for 38% (171/449) of patients in this study. LV dysfunction was present in approximately two-thirds of this patient population (mild-to-moderate dysfunction in 33% and severe dysfunction in 29% of patients). The majority of patients (78%) were concomitantly administered antiarrhythmics, half (50%) antihypertensives and 12% inotropic agents. For patients on these co-medications, the SmPC calls for careful titration of landiolol since co-administration can result in excessive suppression of cardiac function, atrioventricular conduction abnormalities and increased risk of bradycardia

and hypotension. A high rate of concomitant medication use in the patient population may partly explain the low doses of landiolol observed in this study.

The median landiolol infusion duration was 8.9 h. In approximately one-third of cases (33%), landiolol was administered for more than 24 h, which is longer than recommended by the SmPC. Patients suffering from non-compensatory sinus tachycardia were administered landiolol for the longest time (median: 31 h), when compared to other indications. The shortest duration of landiolol administration was observed in the ECU with the median of 2 h, reflecting the nature of emergency care treatment. Severe concomitant illnesses such as sepsis, heart failure and myocardial infarction prolonged landiolol administration when compared to patients without these conditions. Patients who were administered landiolol without the concomitant use of antiarrhythmic agents had a longer duration of infusion than those who used concomitantly antiarrhythmic agents (17 vs 7 h), while the opposite result was observed for inotropic agents (7 vs 27 h).

The highest starting doses were administered in the ECU with a median dose of 10 µg/kg/min, followed by the ICU and normal hospital ward with a median dose of 4 and 3 µg/kg/min, respectively. Patients with sepsis, heart failure and myocardial infarction were administered lower initial doses than the patients without these concomitant illnesses. The median highest dose was 10 µg/kg/min and the median lowest dose was 4 µg/kg/min. The median infusion doses were rather low when compared to the doses recommended by the SmPC (ranging from 1 µg/kg/min for the patients with cardiac dysfunction to the bolus dose of 100 µg/kg/min) and the treatment regimen recommended by the European Society of Cardiology (Hindricks et al., 2021) but may reflect the significant number of patients with LV dysfunction included in this study. One patient received a bolus dose of 100 µg/kg/min, and no patient received a higher dose than recommended by the SmPC. Lower doses reflect the user population in this study, which included patients with frequent comorbidities and concomitantly administered medication such as antiarrhythmic, inotropic and antihypertensive agents. The highest doses of landiolol were administered to patients in the ECU, while the doses administered in the ICU and normal hospital ward were comparable. Patients with sepsis, heart failure and myocardial infarction were administered lower doses than the patients without these concomitant illnesses. Patients with concomitant use of antiarrhythmic agents were administered higher doses of landiolol than the patients without, while slightly lower doses of landiolol were used in patients with concomitant use of inotropic agents.

Repeat treatment occurred in 24 patients (5%), with 20 participants receiving 2 treatments each and 4 participants receiving 3 treatments each. Patients received a median total dose of 300 mg per treatment. The subgroup analysis revealed that the highest total dose was administered in the ICU (median: 540 mg), for the treatment of non-compensatory sinus tachycardia (median: 981 mg), and in association with sepsis (median: 498 mg). Importantly, no evidence of landiolol overdose, medication errors, or inappropriate repeat prescribing in actual clinical practice was found. The high variability in usage data may also arise from regional differences in clinical practice and health care systems management (eg. diagnostic criteria, prescribing practices or reimbursement policies) across centers or countries where the real-world data was collected.

Although landiolol was administered equally via central and peripheral lines in the whole population, the central line was the preferred route in intensive care, whereas the peripheral line was favored in emergency care.

Landiolol treatment was considered effective and thus discontinued in 67% (321/477) of cases. This result was driven by the patients in the ICU and normal hospital ward, with 80% (200/250) and 77% (30/39) effectiveness of the treatment, respectively. The treatment was effective and thus discontinued in 48% (89/185) patients in the ECU. This result is also visible in a reduction in HR upon treatment (mean ± SD HR before infusion: 132 ± 27 bpm and after infusion: 103 ± 25 bpm).

The efficacy of landiolol treatment in controlling HR was high. Most of the patients (74%) achieved HR control ≤110 bpm or >20% reduction within 4h after landiolol treatment discontinuation when compared to the baseline. Furthermore, 50% patients achieved HR control ≤90 bpm within 4h after landiolol treatment discontinuation. The highest proportion of patients with HR control was observed in patients with non-compensatory sinus tachycardia. Overall, tachycardia worsens cardiac performance in patients with cardiac dysfunction because of a decrease in diastolic filling and an increase in myocardial oxygen demand. It is worth pointing out that the target HR will depend on the patient characteristics, symptoms, LVEF value, and hemodynamics. A lenient rate control (HR target <110 bpm) is an acceptable initial approach, unless symptoms call for stricter rate control (Hindricks et al., 2021; Joglar et al., 2024). Approximately 42% patients showed recovery of normal sinus rhythm within 4h after landiolol treatment discontinuation, with the highest recovery rate in non-compensatory sinus tachycardia patients, which is however the condition mostly characterized by normal sinus rhythm. The percentage of patients with rhythm recovery was 37% and 33% in atrial fibrillation and atrial flutter, respectively. These efficacy results are consistent with those obtained in several randomized controlled trials. More specifically, landiolol has been shown to reduce HR in patients after cardiac surgery (Sakamoto et al., 2012; Li et al., 2015) and acute myocardial infarction (Hanada et al., 2012), as well as in patients with LV dysfunction (Nagai et al., 2013) and sepsis (Kakihana et al., 2020). Subgroups analyses based on concomitant administration of antiarrhythmic and inotropic agents did not show any substantial differences in efficacy between patients with and without these concomitant treatments.

The safety analysis in the user population revealed that 79 patients (18%) experienced 123 AEs. Of these, 56 were considered SAEs. Importantly, none of the AEs was assessed to be related to the landiolol treatment. 6 AEs led to discontinuation of the treatment in 6 patients (1%). Patients' subsequent care needs to manage AEs included electrical cardioversion (5%), cardiopulmonary resuscitation (1%) and cardiac ablation (0.7%). Most AEs were classified as cardiac disorders (72 events in 49 patients). The typical AEs for beta-blockers, hypotension and bradycardia, were reported in 9 (2%) and 1 (0.2%) patients, respectively. The recording of MACEs was explicitly solicited in the eCRF by event type at all visits (except Visit 1). Overall, 112 patients (25%) experienced 113 MACEs. Within 6 months of landiolol treatment, 110 out of 449 (25%) patients had died, of which 40 participants from cardiovascular death and 70 participants from other causes of death. The highest death rates were recorded in the ICU (35%), for the indication of non-compensatory sinus tachycardia (43%), and for patients with sepsis at start of treatment (57%). None of the 113 MACEs was assessed to be related to the landiolol treatment. In previous studies, landiolol showed a relatively low risk of hypotension and bradycardia (reviewed in Nasoufidou et al., 2024). These low incidence numbers reaffirm

the favorable safety profile of landiolol, a highly cardio-selective beta-blocker with rapid onset of action and short elimination time, for which any AEs can be quickly restored by lowering the dose or discontinuing administration. This real-world data shows no new safety signals resulting from intravenous landiolol use in the whole population or in the different subgroups analyzed.

11.2. Limitations

A limitation of this study is the considerable amount of missing data. For example, some potential confounders in the analysis, such as the initial reason for hospital admission or disease severity, were not recorded in the eCRF. The extent of missing data varies among datasets, ranging e.g. from 1% for infusion duration to 62% for baseline LV function.

In part due to the observational nature of the study, AEs were not as exhaustively or consistently reported as it would be expected in a clinical trial. For example, as per by-patient AE listing, 6 patients experienced an AE leading to discontinuation of the treatment. However, when asked for the reason for discontinuation of treatment in another section of the eCRF, AEs were stated as the reason 9 times. In addition, there are 5 cases where AE was not selected as the reason for discontinuation even though the actual reason given matches AE criteria and should have been reported as such.

The efficacy of the treatment was assessed within 4 hours after landiolol discontinuation, therefore the patients who achieved HR control during the treatment but did not maintain it after the discontinuation of landiolol, were not included among responders. This could lead to underestimation of the response rates. Assessment of the time to HR control was dependent on the frequency of HR measurements during and after treatment, which was often sparse and differed between sites. Therefore, the values reported for this endpoint do not correlate with the prompt onset of action of landiolol, which typically occurs within a few minutes. Another limitation is information bias. Certain study variables may have been inaccurately measured. Although extensive data verification and cleaning was performed for the primary endpoint, some secondary endpoints did not receive the same level of attention. For instance, the ambiguous labeling of visits dates as „Date and time of patient admission” (for Visits 3-5) may have invalidated the proper assessment of the secondary endpoint “length of hospital stay”.

This study included the patients with supraventricular tachycardia but does not provide information about patients e.g. with ventricular tachycardia or ventricular flutter, for whom landiolol is recommended in treatment guidelines (Zeppenfeld et al., 2022) and used off-label in the clinical practice.

11.3. Generalizability

In this study, we included all adult patients who received landiolol for any of the indications listed in the SmPC. Patients either signed the informed consent, if able to give consent, or were covered by a waiver, if incapable of consenting during hospitalization. By using a waiver, we extended the patient population to include those with poor health status or a worse prognosis at the start of landiolol treatment.

In addition, a broad range of hospital settings (ICU, ECU and normal hospital ward), use of concomitant medications (mainly antiarrhythmics and antihypertensives) and concurrent illnesses (sepsis, myocardial infarction, and heart failure) are well represented in this study.

This population diversity enhances the study findings' applicability to clinical practice, surpassing that of previous clinical trials on landiolol use.

Furthermore, the study was conducted across 17 sites in 8 European countries. This broad coverage ensures a good representation of treatment regimen strategies following different medical and institutional guidelines.

Altogether, the study population and design are well-suited to address the study objectives.

11.4. Conclusions

Across Europe, patients are being administered intravenous landiolol in line with approved labeling and the European Society of Cardiology (ESC) guidelines. Dosing of landiolol in clinical routine practice corresponded to the recommendations in the SmPC. The median duration of landiolol infusion was 8.9 hours, with a median peak dose of 10 µg/kg/min. This usage reflects the high number of patients with cardiac dysfunction in this study and is consistent with the recommendations in the SmPC which recommends dose of 1-10 µg/kg/min. Landiolol provided HR control in the majority of patients while minimally impacting systemic hemodynamics. Tachycardia was well managed by landiolol intervention across supraventricular tachycardia subtypes. Landiolol was generally well tolerated, with a low incidence of hypotension (2%) and bradycardia (0.2%), highlighting its favorable safety profile and the effectiveness of the risk management measures. There were no AEs or MACEs related to landiolol. These findings have no impact on the benefit-risk balance of the product, or the information included in the SmPC. By reflecting a more comprehensive experience on the drug use at a larger scale, this real-world data strengthens the evidence base for landiolol in patients with tachycardia of various origin, in various hospital settings, and with other concurrent illnesses or on other concurrent medications.

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13. Appendices

Please see the cover page for a complete list of the documents provided along with this study report.