COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Landiolol Hydrochloride Orpha-Devel 300 mg powder for solution for infusion (landiolol hydrochloride)

NL/H/5509/001/DC

Date: 4 June 2026

This module reflects the scientific discussion for the approval of Landiolol Hydrochloride Orpha-Devel 300 mg powder for solution for infusion. The procedure was finalised on 29 November 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
AF	Atrial fibrillation
AFI	Atrial flutter
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
bpm	beats per minute
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EDMF	European Drug Master File
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
HR	Heart Rate
ICH	International Conference of Harmonisation
i.v.	Intravenous
LAN	Landiolol
LDL202	Landiolol concentrate 20 mg
LDLL300	Landiolol lyophilisate 300 mg
LDLL600	Landiolol lyophilisate 600 mg
MAH	Marketing Authorisation Holder
PBPK	Physiologically Based Pharmacokinetic
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Landiolol Hydrochloride Orpha-Devel 300 mg powder for solution for infusion, from Orpha-Devel Handels und Vertriebs GmbH.

The product is indicated in adults 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.
- Non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention.

Landiolol is not intended for use in chronic settings.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC, which concerns a full (complete dossier) application.

Landiolol hydrochloride has been authorised, as powder for solution for infusion, in Japan since 2002. An extensive clinical program in Japanese subjects has been performed by Ono Pharmaceutical in support of the registration of Onoact 50 for injection in Japan and in the post-licensing phase of the product. The key clinical studies of Onoact have been published and are available in the public domain. The application for Landiolol Hydrochloride Orpha-Devel is mainly based on these published studies. Four bridging studies were performed to show that the published clinical pharmacology, efficacy and safety data obtained for Onoact can be extrapolated to Landiolol Hydrochloride Orpha-Devel and to justify the translation of the results obtained in the Japanese population to the Caucasian population.

In 2016 landiolol lyophilisate 300 mg was approved via the decentralised procedure in several European countries (trade names: Rapibloc, Raploc, Landiobloc, Runrapiq, MAH in the Netherlands (NL/H/3368/001) Amomed Pharma GmbH) with the same indications as the current application.

The concerned member states (CMS) involved in this procedure were Belgium, Ireland, Portugal and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Landiolol Hydrochloride Orpha-Devel is a white to almost white powder for solution for infusion. The product is presented in vials, each vial contains as drug substance 300 mg

landiolol hydrochloride powder equivalent to 280 mg landiolol. Before administration, the powder must be reconstituted as described in SmPC section 6.6. The concentration of the reconstituted solution (content of 1 vial dissolved in 50 mL solution) is 6 mg/mL landiolol hydrochloride.

The excipients are: mannitol E421 and sodium hydroxide E524 (for pH adjustment).

The powder for solution for infusion is packed in colourless glass (type 1) 50 mL vial with a chlorobutyl rubber stopper and an aluminium flip-off seal. The vial is contained in an outer cardboard carton.

II.2 Drug Substance

The drug substance is landiolol hydrochloride, an established active substance not described in any pharmacopoeia (Ph. Eur.). Landiolol, as the hydrochloric acid salt is a white to off-white powder, which is very soluble in water and methanol, freely soluble in DMF, soluble in ethanol and slightly soluble in acetonitrile. Landiolol is a chiral compound having two asymmetric carbon atoms with four possible isomers, the required isomer is the SS-isomer. Landiolol is hygroscopic. The developed manufacturing process provides consistently the same polymorphic form (γ-crystalline form). This has been demonstrated by a single crystal evaluation. However, as the drug substance will be dissolved for the preparation of the drug product, the polymorphic form is not considered for the intended application as a critical quality attribute due to the very high solubility of the drug substance in water. Full documentation on the active substance has been included in the dossier.

Manufacturing process

The synthesis of landiolol hydrochloride consists of several synthetic steps followed by crystallisation/purification steps. No class 1 organic solvents or metal catalysts are used. The starting materials, solvents and reagents are considered acceptable and have adequate tests and acceptable specifications. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specifications are considered adequate to control the quality. Landiolol hydrochloride is not described in any pharmacopoeia, hence the in-house specifications are set by the drug substance manufacturer. In light of the currently available information and in view of the route of synthesis and the various European guidelines, the specifications are considered acceptable. Sufficient information has been provided on analytical procedures and their validations. Batch analytical data demonstrating compliance with the drug substance specifications have been provided for one half-scale batch and three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for four batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 18 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The concentration and the pH of the bulk solution were optimised, and according to the MAH the ratio of landiolol hydrochloride and mannitol is identical to the ratio as applied for the product already approved in the EEA and in Japan. The bulk solution is used to prepare landiolol Hydrochloride 300 mg, powder for solution for infusion, which will be diluted/reconstituted with 50 mL diluent to concentration of 6 mg/mL. Supporting information has been provided on the pH and osmolality of the reconstituted solutions ready for infusion. The reported pH and osmolality ranges are close to the physiological values. Hence, the proposed solutions are acceptable for infusion without increasing the risk of phlebitis. The pharmaceutical development was performed on the product from a manufacturer other that the current manufacturer. Since the quality of the medicinal product obtained with the active substance from both suppliers proved to be comparable, the conclusions of the pharmaceutical development can be bridged to the product produced with the active substance from the current supplier. Overall, the manufacturing process is acceptable and the method for sterilisation has been sufficiently justified.

To support the recommendations in the SmPC for the reconstitution of the product, compatibility studies have been carried out. Compatibility of Landiolol 300 mg lyophilisate with NaCl 9 mg/mL (0.9%) solution, glucose 50 mg/mL (5%) solution, ringer's solution, and ringer-lactate solution has been sufficiently demonstrated.

Manufacturing process

The manufacturing processes is considered to be a non-standard process and consists of the main steps compounding, filtration, filling, lyophilisation, and capping. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches. The depyrogenation cycle used for glass vials is more strict than the Ph. Eur. cycle and the validation report shows acceptable endotoxin log reduction.

Control of excipients

The excipients comply with the specifications of the most recent version of the European Pharmacopoeia with additional tests on microbial contamination and Bacterial Endotoxin Test (BET). The specifications are acceptable.

Microbiological attributes

As the product is sterile, the integrity of the container closure system was investigated to prevent microbial contamination. The container closure system is common for freeze dried powders and suitable for the current drug product. As the stoppers comply with Ph. Eur. and the reconstituted product is a fully aqueous solution with a neutral pH, leaching of additives is not considered relevant.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, identification, assay, degradation products, nitrosamine impurities, uniformity of dosage units, water content, reconstitution time, clarity and colour of reconstituted solution, pH of reconstituted solution, visible particles, sub-visible particles, osmolality of the reconstituted solution and microbial quality (sterility and endotoxins). Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product. Limits for the tests related substances and pH at release and shelf-life differ, this have been adequately justified. Overall, the drug product release and shelf-life specifications are acceptable.

An adequate risk assessment report for nitrosamines has been submitted. Based on this assessment, appropriate tests for the presence of nitrosamines are routinely performed on the final product. Additionally, a risk assessment on elemental impurities in the drug product in accordance with the ICH Q3D (option 2b) Guideline has been conducted. The predicted levels of all the elemental impurities (EIs) under assessment are well below their control threshold (30% of Permitted Daily Exposure (PDE)). Therefore, not testing for elemental impurities at drug product release is considered justified, no further controls are required.

Satisfactory validation data from the analytical methods have been provided.

Batch analytical data three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with the applicable ICH guidelines. Additionally, stability data was submitted through variation NL/H/5509/001/IB/003 (approved on 23-7-2025). Based on the provided stability data, the proposed shelf-life of 3 years is considered acceptable. The labelled storage conditions (modified via variation NL/H/5509/001/IB/006, approved on 27 March 2026) are: 'Keep the vial in the outer carton in order to protect from light. This medicinal product does not require any special temperature storage conditions.'
'For storage conditions after reconstitution of the medicinal product, see section 6.3.'

In-use stability data have been provided demonstrating that the product remains stable up to 24 hours following reconstitution and when stored at 25°C. The conditions stated in the SmPC are: 'Chemical and physical in-use stability after reconstitution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user. Do not freeze.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product, nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Landiolol Hydrochloride Orpha-Devel 300 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The pharmacology program for landiolol was comprised of both primary and secondary pharmacodynamic assessments of landiolol as well as safety pharmacology studies. The non-clinical pharmacology program consisted of studies that demonstrated the specificity and selectivity of landiolol as a β1-adrenoreceptor (β1-AR) antagonist (β1-blocker); the cardioselectivity of landiolol; the evaluation of chronotropic and inotropic effects of landiolol in comparison to other β1-blockers; and evaluation of effects on experimentally induced tachycardia in dogs. Safety pharmacology studies included *in vitro* transfected mammalian cells expressing cloned human hERG (human Ether-a-go-go Related Gene) assay as well as cardiovascular, respiratory, and behavioural functional parameters.

Primary pharmacodynamics

In vitro pharmacodynamics studies have clearly shown that landiolol is a specific and selective β1-adrenoreceptor (β1-AR) antagonist, being more specific than the marketed reference compound esmolol (AOP-Freissmuth 2015, AOP-Freissmuth 2020; ONO 2013). The β1 blocking activity of major human metabolite M1 was approximately 100-fold lower compared to landiolol. With membrane fractions obtained from rat several tissues, it was demonstrated that landiolol has a low affinity for ion channels and receptors other than β-receptor (Iguchi et al., 1992). In tissue samples of papillary muscles, left atrial muscles (β1-AR) and lungs (β2-AR) obtained from male Beagle dogs, cardioselectivity for the β1-AR was demonstrated (Shiroya et al., 1997a).

In perfused heart preparations *ex vivo*, landiolol exerted negative chronotropic effects and was shown to be an ultrashort-acting β-blocker with a dose-dependent recovery time and with a β-blocking activity that was slightly more potent than that of esmolol (Shibata et al., 2012). *In vivo*, animal models in rabbits and dogs confirmed the *in vivo* β1-AR selectivity and the negative chronotropic effect (Iizuka et al., 2004; Ikeshita et al., 2008; Sasao et al., 2001). In addition, landiolol has a rapid onset and offset of effect, indicating that the drug acts as an ultra-short-acting β-blocker, similar to esmolol (Motomura et al., 1998). Moreover, various *in vivo* models provided support for the proof-of-concept of the anti-arrhythmic effects of landiolol (Iguchi et al., 1992; Iizuka et al., 2004; ONO, 2013; Sasao et al., 2001; Shiroya et al., 1997a, Shiroya et al., 1997b; Sugiyama et al., 1999).

Secondary pharmacodynamics

Non-clinical studies on secondary pharmacodynamic effects have shown no membrane stabilizing activity by landiolol, no effect on glucose and lipid metabolic parameters, nor on plasma renin activity (ONO 2013; Shiroya et al., 1997c).

Safety pharmacology

Considering that landiolol is a well-known active substance, marketed in Japan since 2002 and in Europe since 2016, the safety pharmacology has been adequately addressed. Overall, there is no apparent risk of adverse changes to the central nervous system (CNS), respiratory or cardiovascular system after administration of landiolol.

Pharmacodynamic drug interactions

Landiolol can have pharmacodynamic interactions with digitalis preparations, class I antiarrhythmic agents, calcium blockers, anaesthetics, sedative drugs, psychotropic drugs, muscle relaxants, anticonvulsants, suxamethonium chloride, sympathomimetic agents, cholinesterase inhibitors, hypoglemic drugs (ONO 2013; PMDA 2002). This is adequately addressed in the SmPC.

III.2 Pharmacokinetics

The *in vivo* pharmacokinetics and toxicokinetics (TK) of landiolol was studied in rats and dogs. The species and strains used for *in vivo* PK assessment were the same as those used in safety pharmacology and toxicology studies. Furthermore, landiolol has been studied *in vitro* in rat, dog, and human plasma and/or liver homogenates to determine plasma protein binding, metabolism across species, and interactions with cytochrome P450 (CYP) enzymes. The concentrations of landiolol in rat (Tsunekawa et al., 1997a, Tsunekawa et al., 1997b) and dog (Tsunekawa et al., 1997d) plasma samples were either determined by liquid scintillation measurement of ^{14}C-landiolol or by a landiolol HPLC-MS/MS method. In the additional AOP Orphan-initiated toxicity studies performed to supplement existing data, a validated HPLC-MS/MS method using precipitated whole blood was applied.

Absorption

In rats, after single dose administration, the decline of landiolol in plasma was biphasic with a terminal elimination half-life of approximately 30 minutes (Tsunekawa et al., 1997a). In dogs, the terminal elimination half-life of landiolol was 5-6 minutes. Terminal elimination half-life of metabolite M1 in dogs was 160-180 min and of M2 90-150 min. (Tsunekawa et al., 1997d). Clearance of total radioactivity was 419-558 mL/hr/kg in rats. Elimination of landiolol was very rapid in dogs with clearance of 69-83 mL/min/kg (Tsunekawa 1997b). Distribution volume of landiolol in dogs was 370 mL/kg. Distribution volume in rats was not provided. AUC increased approximately dose-proportional in rats and dogs. No sex effects were visible in rats (Tsunekawa 1997a). In dogs, only males were investigated. Following repeated dosing in rats for 7 days at 1 mg/kg, AUC was similar to single dose AUC (Tsunekawa et al., 1997a, Tsunekawa et al., 1997b, Tsunekawa et al., 1997c).

In dogs, during intravenous (i.v.) infusion, plasma levels and AUC of landiolol were higher when anaesthesia was applied, than without anaesthesia. For the metabolites, the difference was smaller (Braswell & Kitz, 1977). According to published literature, blood flow in the liver and hence, hepatic metabolic clearance is reduced in the presence of anaesthesia. In the

clinical setting, plasma concentrations of landiolol may therefore be higher when landiolol is infused during operations when anaesthesia is present.

Distribution

Protein binding of landiolol (0.1 – 50 µg/mL) was low in all investigated species. *In vitro* protein binding was 2.7 - 5.3% in rat serum, 14.7 – 21.3% in dog serum, 1.5 – 7.0% in human serum and 2.4 – 11.0% in human serum containing 4.3% HSA (human serum albumin). Slight concentration dependence was observed in human blood with the highest protein binding (but still low) at 50 µg/mL. *In vivo* protein binding in rats was slightly higher than *in vitro*, but still low (15.1 – 15.9%) (Tsunekawa et al., 1997c).

Blood to plasma distribution was not determined in a separate experiment but could be derived from the tissue distribution. After i.v. bolus administration of 1 mg/kg of the ^{14}C-landiolol HCl to rats, blood to plasma distribution of radiolabelled drug-related material was 0.5 - 0.6 up to and including 1 hour after administration, indicating no distribution to red blood cells. Distribution to red blood cells was found at later time points (blood to plasma distribution was 1 at 4 hours (h) and 5 at 24 h after dosing). However, at these time points plasma concentrations were already low and it is not expected to have a significant impact on pharmacokinetics (Tsunekawa et al., 1997a).

Highest concentrations of drug-related radioactivity were found in lungs, liver, kidney, uterus, ovary and urinary bladder. At 24 h after dosing, levels were below the limit of detection or only slightly above, except after 7 days of daily bolus injections, where still measurable amounts were found in liver and kidney at 24 h after the last dose. Drug-related radioactivity was distributed to the brain, but at low levels. A significant level was found in the placenta, but foetal levels were low (Tsunekawa et al., (1997a).

Metabolism

The metabolism of landiolol was primarily investigated *in vivo* in rats and dogs. The main metabolite M1 is formed by hydrolysis of landiolol which starts immediately after landiolol enters the plasma. M2 is produced by β-oxidation of M1 (Tsunekawa et al., 1997c).

In rats, at 5 – 30 min after bolus injection landiolol comprised only 1.6 – 2.1% of total radioactivity in blood. M1 was 81.8 - 86.9% of total radioactivity in blood. 11.5 – 16.1% was unknown. It is not known whether most of this was M2 or whether there were also other, minor, metabolites. M1 was however the major metabolite, as it is in humans. From the excretion data in urine, it seems clear that both M1 and M2 are major metabolites in dogs. In urine, up to 24 h after dosing, 2.7% of the dose was landiolol, 38.1% M1, and 40.5% M2 and total recovery in urine after 24 h was 81.3%. This does not add up to 100%, but a small percentage of the dose must have been excreted in the faeces and at 24 h after dosing most likely not the whole dose was excreted yet. Although the information regarding metabolism was rather concise, it seems clear that there are no other relevant metabolites than M1 and M2 (Tsunekawa et al., 1997a; Tsunekawa et al., 1997b; Tsunekawa et al., 1997c, Tsunekawa et al., 1997d).

In a 7-day experiment in rats, it was observed that landiolol did not cause enzyme induction in the liver. No effect was found on liver microsomal protein content, cytochrome P450 content and glucose-6-phosphatase, aminopyrine N-demethylase, aniline hydroxylase, NADPH cytochrome C reductase, and NADH ferricyanide reductase activities (Tsunekawa et al., 1997b).

Excretion

In rats, approximately 85% of total radioactivity was excreted in urine and 15% in faeces. In dogs, at least 80% (landiolol + M1 + M2) was excreted in the urine. This is similar to humans, where urine is also the main route of excretion. Landiolol and metabolites were excreted via the milk of rats (Tsunekawa et al., 1997a).

Pharmacokinetic drug interactions

Since the initial approval of landiolol as Onoact (Japan, 2002) and subsequently as Rapibloc (EU, 2016) extensive clinical experience for the application of landiolol in the approved indications and patient populations has been gathered. There were no signs or adverse events reported that would indicate a potential drug interaction (e.g., by inhibition of transporters) with the various drugs concomitantly administered in the patient population during the preoperative until postoperative period. Taking into account the clinical experience with landiolol, the pharmacokinetic drug interactions have been sufficiently addressed.

III.3 Toxicology

The non-clinical safety program of landiolol consists of published non-clinical studies on landiolol and the landiolol-containing drug product, Onoact. In addition, AOP Orphan conducted a tailored non-clinical study program during development of the already approved drug product Rapibloc in order to complement existing and published information.

The non-clinical safety of landiolol was evaluated in rats, rabbits and dogs using either i.v. bolus injection (rat, rabbit, and dog) or continuous i.v. infusion (dog) for administration of landiolol up to multiples of the therapeutic exposure in a battery of toxicology studies. The species and strains used for *in vivo* toxicity assessment were the same as those used in pharmacology, safety pharmacology and pharmacokinetic studies. Furthermore, the genotoxic properties of landiolol have been investigated *in vitro* in three bacterial reverse mutation assays, a mouse lymphoma test and an *in vivo* micronucleus test in rats. Three local tolerance studies as well as three impurity qualification studies were performed in rats.

Single dose toxicity

A GLP-compliant single dose toxicity study in rats (continuous 24-h infusion; studies conducted by AOP Orphan study nr. 610774) was conducted. No mortality and no significant adverse effects were observed with landiolol infusion up to 1000 mg/kg. Based on AUC, the exposure to landiolol in this study was lower than the human exposure. M1 and M2 were major metabolites in rats, with systemic exposure of M1 up to approximately 160-fold greater than landiolol.

Repeat-dose toxicity

In 4-week bolus i.v. studies, mortality occurred at 100 mg/kg/day in rats as a result of acute toxicity. In rats, bradypnea / dyspnea, tremor, loss of righting reflex and injection site reactions were observed at 100 mg/kg/day. In dogs, vomiting, nausea and diarrhoea were observed at ≥25 mg/kg/day (Iguchi et al., 1992; Yamaguchi et al., 1997a; Yamaguchi et al., 1997b; Yamaguchi et al., 1997c).

In rats, the exposure to landiolol + metabolites following 24-h infusion was far below the human exposure. Repeated bolus administrations to rats for up to 28 days resulted in

estimated exposures exceeding human exposure. In dogs, the exposure following a 28-day continuous infusion exceeded the human exposure as well. No target organ toxicity was observed and from β-blockers it is known that in general they do not induce target organ toxicity. Moreover, animals were treated up to 4 weeks which exceeds treatment period with landiolol in clinical practice. Overall, the toxicology data can be considered sufficient.

Genotoxicity

Landiolol was not genotoxic in the Ames test, mouse lymphoma assay and *in vivo* micronucleus test in rats. The exposure in the *in vitro* studies and in the rat micronucleus study was sufficient (studies conducted by AOP Orphan: study No. 787325, 795100, 794018, 787330 and 790584).

Carcinogenicity

As landiolol is intended for short-term use only, it is endorsed that no carcinogenicity studies were performed.

Reproductive and developmental toxicity

Fertility

There were no effects on reproductive performance in male or female rats at clinically relevant exposures (Nishimura et al., 1997a, Nishimura et al., 1997c, Nishimura et al., 1997b; Nishimura et al., 1997d).

Embryo-foetal development (EFD)

Landiolol caused no adverse effects on the embryofoetal development in rats (Nishimura et al., 1997d) and rabbits (Nishimura et al., 1997c). In the rat study, the experiment was continued up to the reproduction of the F1 generation and adverse effects were seen on the post-natal development in F1 rats: decreased survival and decreased ossification on post-natal day 4 and an increase in early resorptions following the reproduction of the F1 animals. The clinical relevance of this may be limited because in clinical practice, landiolol will only be administered short-term.

Peri- and postnatal development (PPND)

In the PPND study in rats, landiolol caused decreased body weight gain in high-dose F1 pups as well as decreased survival and decreased ossification on post-natal day 4 in high-dose F1 pups. This occurred in the presence of maternal toxicity because 3 high-dose dams died during the lactation period and a decrease in food consumption and body weight was observed in high-dose dams during lactation (Nishimura et al., 1997d).

No toxicokinetic measurements were performed in these studies and therefore there is no information regarding the level of exposure in these studies. Based on pharmacokinetic data in the rat, the exposure in the rat studies can be expected to have been below the human therapeutic exposure.

Local tolerance

Regarding local tolerance, landiolol as lyophilised formulation and as concentration formulation were in general well tolerated in rabbits at intended or unintended application sites.

Other toxicity studies
With regard to impurities, M1 can be considered qualified because it is a major metabolite in rats and as such it has been investigated in toxicology studies and genotoxicity studies.

A structure-activity relationship (SAR) analysis was conducted on several impurities using Derek Nexus and Leadscope in silico systems. The overall weight of evidence from the SAR analyses revealed no relevant alerts for genotoxicity.
In none of the three rat impurity qualification studies, new significant general toxicity was observed. In study 510638, the impurities were pooled in the absence of landiolol itself. In studies 612546 and 504598 landiolol was also administered to the animals. The absolute levels in mg/kg infused to the rats at the maximum doses were above maximum absolute levels to which humans can be exposed at the proposed specifications. The impurities have therefore been sufficiently qualified, especially considering the fact that landiolol is not intended for chronic use.

Haemolysis
Haemolysis of landiolol (Rapibloc 300 mg; study 312069) was evaluated for the potential of haemolysis. Landiolol was not haemolytic in rat and human blood.

Phototoxicity
No phototoxicity studies were performed, which is accepted.

III.4 Ecotoxicity/environmental risk assessment (ERA)

For the Ecotoxicity/environmental risk assessment, the MAH has submitted the following study results.

Summary of main study results Phase I

Substance (INN/Invented Name):	*landiolol*		
CAS-number (if available):	*133242-30-5 (landiolol); 144481-98-1 (landiolol hydrochloride)*		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD 107	*1.14 at pH 10*	Potential PBT: N

Phase I

Parameter	Value	Unit	Conclusion
$PEC_{sw,\ refined}$ *(prevalence / treatment regime)*	*0.0398*	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Conclusions on studies for landiolol:
As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Landiolol to the environment. The MAH commits to conduct the requested phase II Tier A studies and proposed an acceptable schedule. The MAH is requested to provide an updated ERA and the original study reports when all studies are completed and the ERA is finalised.

A bioaccumulation potential is not indicated based on the log KOW < 4.5. A definitive PBT/vPvB assessment is not required.

III.5 Discussion on the non-clinical aspects

The MAH relied on the comprehensive scientific literature and collected a sufficient amount of information on pharmacological and toxicological properties of the active substance. There are no objections against approval. The MAH committed to submit the final ERA post-approval. Overall, the submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Landiolol Hydrochloride Orpha-Devel 300 mg is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Four bridging studies were performed to show that the published clinical pharmacology, efficacy and safety data obtained for Onoact can be extrapolated to Landiolol Hydrochloride Orpha-Devel 300 mg and to justify the translation of the results obtained in the Japanese population to the Caucasian population.

Clinical studies
The MAH has submitted three PK/PD studies in healthy Caucasian subjects, and one patient study in Caucasians with AF or AFl (table 1) and conducted a physiology-based PK study sponsored by AOP Orphan Pharmaceuticals. Furthermore, the application relies on published literature on the pharmacology, efficacy and safety of Onoact, a lyophilised 50 mg formulation of landiolol (ONO-1101), which has obtained Marketing Authorisation (MA) in Japan in 2002.
All four studies sponsored by AOP Orphan Pharmaceuticals included PK/PD assessments of Landiolol, i.e. Onoact and Landiolol lyophilisate 600 mg and Landiolol concentrate 20 mg, in a Caucasian population. An overview of these clinical studies is presented in table 1.

Table 1: Overview of AOP-sponsored studies with Landiolol

Study/ type	Population (number of subjects) with Landiolol	Administration regimen	Treatment (doses, duration)
CPA368-10* *PK/PD study of Onoact versus esmolol*	Caucasian Healthy subjects; N=16 (8 m/8 f)	Short-term infusion	**Onoact 50**: 10 µg/kg/min, 60 min Esmolol: 50 µg/kg/min, 60 min Two treatment periods, cross-over design, dobutamine infusion in both groups.
CPA410-12* *PK/PD study of Landiolol concentrate 20mg (LDL202), esmolol and Onoact*	Caucasian Healthy subjects; Pilot phase N=3 (2 m/ 1 f) Main phase N=12 (5 m/7 f)	Bolus dose	Pilot phase: **Landiolol concentrate 20 mg (LDL202)**: bolus of 300 µg/kg or placebo (saline). Main phase (increasing bolus doses in 1-hour intervals): **Landiolol concentrate 20 mg (LDL202)**: bolus of 100 µg/kg, 200 µg/kg, 300 µg/kg **Onoact 50**: bolus of 100 µg/kg, 200 µg/kg, 300 µg/kg Esmolol: bolus of 500 µg/kg, 1000 µg/kg, 1500 µg/kg Three treatment periods, cross-over design.
CPA422-12 *PK/ safety study of Landiolol lyophilisate 600mg (LDLL600) versus esmolol*	Caucasian Healthy subjects; N=14 (7 m/7 f)	Long-term dose escalation infusion	**Landiolol lyophilisate 600 mg (LDLL600)**: Dose initiation at 10 µg/kg/min for 2 hours, then 20 µg/kg/min for 2 hours, and 40 µg/kg/min for 20 hours Esmolol: 50 µg/kg/min 2 hours, then 100 µg/kg/min 2 hours and 200 µg/kg/min for 20 hours.
LDLL600.201 *PK/PD study of Landiolol lyophilisate 600mg (LDLL600) two different regimens*	Caucasian Patients with tachycardic AF or AFl; N=20 (12 m/ 8 f)	Long-term infusion	**Landiolol lyophilisate 600 mg (LDLL600)** Bolus + maintenance dose group: 100 µg/kg for 1 min, followed by 40 µg/kg/min for max 210 min Maintenance only dose group: 40 µg/kg/min for max 210 min Mean duration: 102 and 159 min with bolus + maintenance and maintenance only dosing, respectively.

AF=atrial fibrillation, AFl=atrial flutter, f=female, m=male, N=number of subjects, PD=pharmacodynamic, PK=pharmacokinetic.

* cross-over studies, i.e. subjects received all study drugs in a cross-over design.

Please note that the clinical studies were conducted with the Landiolol lyophilisate 600 mg formulation or the Landiolol concentrate, the Landiolol lyophilisate 300 mg formulation was not used in clinical studies.

Physiologically Based Pharmacokinetic (PBPK) modelling study

The PBPK modelling study conducted by AOP Orphan Pharmaceuticals integrated literature data from Onoact studies as well as own clinical data from the four AOP-sponsored studies. The PBPK modelling study simulated PK values for Landiolol in two populations (Caucasians and Japanese) with varying health status (healthy subjects, patients with tachycardia/reduced cardiac indices, patients with altered metabolic enzyme blood concentrations), and overall provided evidence for Caucasian / Japanese comparability.

Paediatric Investigation Plan (PIP)

For this application, a request for a partial PIP Compliance check has been submitted in the MAH's own name for the proposed product with the invented name "Landiolol Hydrochloride Orpha-Devel" before submission of the decentralised procedure in subject. For this partial PIP Compliance Check the MAH Orpha-Devel Handels und Vertriebs GmbH referred to the PIP issued for AOP Orphan Pharmaceuticals GmbH, number EMEA-001150-PIP02-13-M04. This has been accepted by the EMA and is in compliance with the general requirements for provision of a PIP or PIP Compliance Check in a new decentralised procedure. The assessment was carried out by EMA and following the positive outcome the compliance report with the decision number EMA/65325/2022 was issued. This document was already submitted as part of the initial submission of the procedure in question.
Subsequently, a Request for Modification (RfM) of the Paediatric Investigation Plan (PIP EMEA-001150-PIP02-13-M05) was approved.

Ongoing studies

In addition to the four completed studies, two clinical studies with landiolol lyophilisate are currently ongoing (table 2). The first one is a paediatric study in patients with SVT that is part of the paediatric investigational plan (PIP) as agreed with EMA´s paediatric committee (PDCO). The second is a study in patients with septic shock and associated tachycardia, in which landiolol will be administered for up to 28 days.

Table 2: Ongoing clinical studies with Landiolol (AOP-sponsored studies)

Study/ type	Population (number of subjects) with Landiolol	Age (years)	Administration regimen	Treatment (doses, duration)
LDLL300.301 PK/PD/safety study of Landiolol in paediatric patients (LANDI-PED)	Planned study population: 120 patients 0-17 years of age with SVT.	0-17 years	Long-term infusion	**Landiolol lyophilisate 300 mg** Initiation with 5 µg/kg/min, up-titration every 30 min up to 40 µg/kg/min (10, 20, 40 µg/kg/min). Maintenance dose for 210 min. Prolongation up to 24 hours if medically indicated and safe.
LDLL300.401 Phase IV, randomised, controlled study of Landiolol in patients with septic shock (LANDI-SEP)	Planned study population: 200 patients with septic shock and persistent tachycardia (≥95 bpm) despite hemodynamic optimisation randomised 1:1 to	> 18 years of age	Long-term infusion	**Landiolol lyophilisate 300 mg** Initiation with 1 µg/kg/min, up-titration up to 40 µg/kg/min until HR target of 80-94 bpm is reached. Infusion of maintenance dose until vasopressor discontinuation (maximum 28 days).

Bpm=beats per minute, HR=heart rate, SVT=supraventricular tachycardia.

Due to slow enrolment in study LDLL300.301 a prediction for the availability of the final study results is currently not possible. If agreed by PDCO, a proposed modification to the PIP projects final study results for Q2/2023. Results for study LDLL300.401 (LANDI-SEP) are expected for Q2/2022.

Note: at the time of writing this PAR, the ongoing studies had been completed and submitted.

- A full PIP compliance check has been conducted. The studies in accordance with the approved PIP EMEA-001150-PIP02-13-M05 were submitted. The effectiveness and safety of landiolol in paediatric patients were assessed with the pivotal prospective study LANDI-PED and the retrospective study LANDI-NEONATE. Please refer to the public assessment report NL/W/0053/PdWS/001, Article 46 for Landiolol hydrochloride, 300 mg powder for solution for infusion. The paediatric worksharing procedure was finalised without changes to the product information.
- The results of the study LANDI-SEP were submitted through the variation Type II NL/H/5509/001/II/002. The variation has been approved. Please refer to the table with the overview of variations on page 31 and Annex I on page 33 of this PAR.

IV.2 Pharmacokinetics

The MAH submitted three PK / PD studies in healthy Caucasian subjects, and one patient study in Caucasians with AF or AFl (table 1) and conducted a physiology-based PK study sponsored by AOP Orphan Pharmaceuticals. Additionally, a total of six published PK studies with Onoact have been submitted (Nakashima and Kanamaru, 2000; Murakami et al., 2005; Atarashi et al., 2000; Wang et al., 2014; Takahata et al. 2005; Matsumoto et al., 2012).

Formulation development

Landiolol lyophilisate 300 mg (LDLL300) is a sterile lyophilised powder containing 300 mg landiolol, and an equal amount of mannitol. Prior to use, the powder has to be reconstituted. In the development process of landiolol different formulations were developed: a lyophilised powder, landiolol lyophilisate 600 mg (LDLL600) and a liquid formulation containing 20 mg landiolol, landiolol concentrate 20 mg (LDL202).

Methods

In the submitted PK/PD studies, validated HPLC-methods were used to detect landiolol and the M1 and M2 metabolites in whole blood. Only a summary of the applied bioanalytical and validation methods has been presented.
Analytical methods used in the submitted publications are sufficiently described.

A Physiologically Based Pharmacokinetic (PBPK) model was submitted to predict the pharmacokinetic variables of landiolol to some extent. The results of the simulations seem to be reliable, however, only marginal information on the precision and validation was submitted. Overall, the statistical methods used throughout the publications and conducted trials are considered acceptable.

Exposure

One phase 2 study was conducted to evaluate the pharmacokinetics of Landiolol in patients.

Study LDLL600.201 evaluated the pharmacokinetics of Landiolol in the Caucasian subjects with AF or AFL (N=20). Subjects received:

- Continuous infusion (CI) of 40 µg/kg/min in the “alternative” dosing scheme (maximal total duration of 210 min).
- Bolus infusion (B) of 100 µg/kg/min for one minute and then continuous infusion (CI) of 40 µg/kg/min in the “conventional” dosing scheme (maximal total duration of 211 min).

When dose changes were corrected to a standard dose, it became apparent that both dosing schemes provided stable dose 20 min. after treatment start. After discontinuation of infusion, landiolol concentrations decreased rapidly with both dosing schemes. PK parameters, based on a non-compartmental model, are summarised in table 3.

Total and maximum exposure were higher in the bolus + maintenance than in the maintenance only dosing group. Clearance (CL) and volume of distribution (V_d) were higher in the maintenance only than in the bolus + maintenance dosing group. Half-life and t_{max} were similar for the two dosing regimens.

Table 3: Pharmacokinetic parameters of Landiolol (bolus + maintenance versus maintenance only dosing scheme) in study LDLL600.201 (PPS population)

	Landiolol (bolus + maintenance dosing) N=9	**Landiolol (maintenance only dosing) N=8**
C_{max} (ng/mL)	2247 (779)	1121 (297)
$AUC_{0-\infty}$ (ng.h/mL)	2072 (1671)	1761 (1218)
$t_{1/2}$ (min)	5.0 (0.7)	5.1 (1.6)
t_{max} (h)	0.50 (0.20, 3.17)	0.75 (0.13, 3.17)
CL (mL/kg.min)	32.75 (7.73)	49.27 (13.37)
Vd (mL/kg)	233.8 (48.5)	353.0 (144.0)

Mean (SD) are presented for all values, except for tmax which is presented as median (range).
AUC0-∞=area under the concentration curve from time zero to infinity, CL=clearance, Cmax=maximum concentration, N=number of subjects, n=number of available values, PPS=per protocol set, SD=standard deviation, t1/2 =half-life, tmax=time to Cmax, Vd=volume of distribution.

Three phase 1 studies in healthy volunteers were conducted to characterise the pharmacokinetics of landiolol and its two inactive metabolites, M1 and M2; Landiolol lyophilisate 300 mg formulation was not used in these clinical studies;

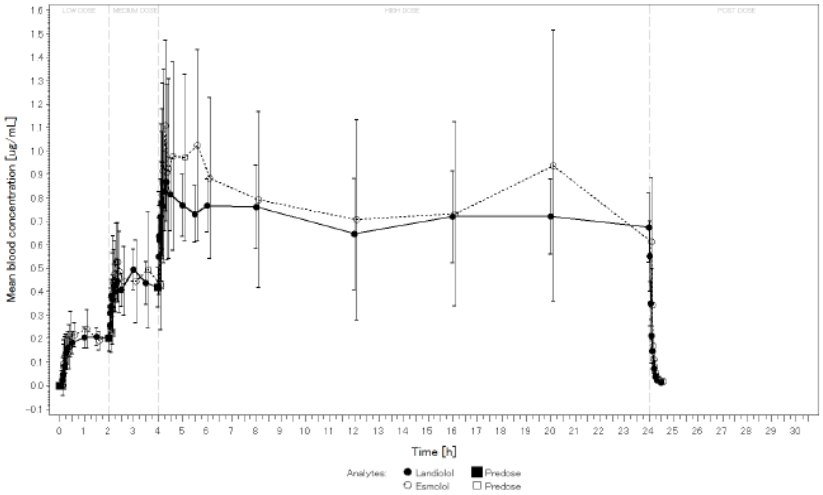
Study CPA368-10 estimated and compared pharmacokinetic parameters of landiolol (Onoact50) and esmolol in Caucasian subjects. Maximum blood concentrations were higher for Landiolol than for esmolol with 191 and 162 ng/mL, respectively, and were reached at 36 and 24 min for Landiolol and esmolol, respectively. Both products had a short $t_{1/2}$ (3.5 and 3.7 min, respectively).

Study CPA410-12 showed that after bolus administration of Rapibloc 20 mg/mL concentrate for solution for injection and Onoact 50 a comparable exposure to landiolol was achieved. The C_{max} and AUC values after 0.1 mg/kg, 0.2 mg/kg and 0.3 mg/kg bolus injections are comparable between both products.

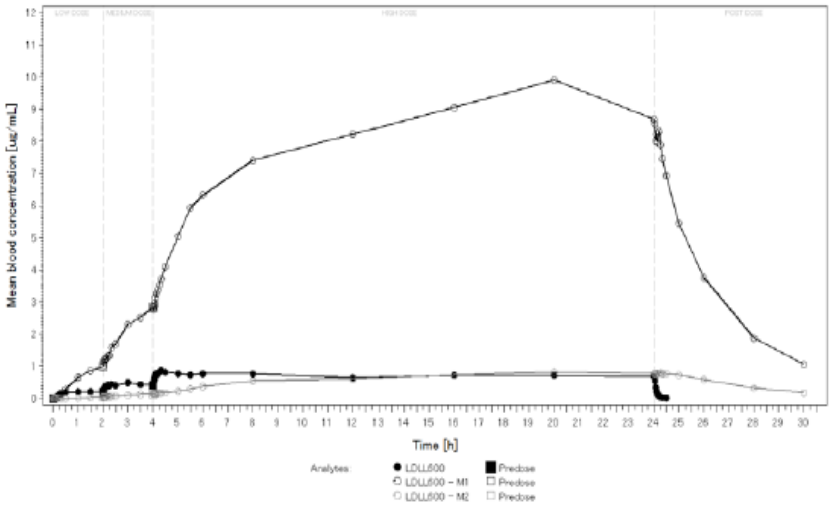
Study CPA422-12 characterised the pharmacokinetics landiolol and its metabolites following administration of Rapibloc Lyo 600 mg powder for solution for infusion (after sequential continuous infusion at low dose (10 µg/kg/min for 2 hours), medium dose (20 µg/kg/min for 2 hours) and high dose (40 µg/kg/min for 20 hours)).

Figure 1 (A & B): Mean blood concentration-time curves of landiolol (A) and its two main metabolites (B) after sequential continuous infusion of 10 µg/kg/min for 2 h followed by 20 µg/kg/min for 2 h and 40 µg/kg/min for 20 h); study CPA422-12.

6A



6B



With use of the PBPK model, the dosing of Rapibloc Lyo with the initial bolus injection proposed in the SmPC was simulated. Also, the pharmacokinetics of the 80 micrograms/kg BW/min dose has been simulated using the model. The submitted simulations given in the report of the model were in general in good agreement with the observed data for the different dosing regimens and in different study populations and were considered acceptable. PBKP modelling has some limitations, due to high interindividual variability of some physiological parameters, PBPK simulations should be interpreted with caution.

Distribution

The apparent volume of distribution of landiolol is about 3 l/kg and for the main metabolite 0.3 l/kg. The half-lives for the parent and the main metabolite are 3.5 minutes and 1.6 hours, respectively. The protein binding for landiolol is low (< 10%) and dose dependent.

Elimination

As landiolol is rapidly metabolised, only 10% of the dose is excreted in urine. The metabolites are also mainly excreted in urine and 90% is excreted within 24 hours. Landiolol is not considered to be subjected to significant active renal secretion as its low molecular weight is far below the molecular weight cut-off for glomerular filtration.

Metabolism

Landiolol is metabolised by carboxylesterase in liver and pseudocholinesterase in plasma mainly into two metabolites M1 and M2. The β1-blocking activity of landiolol metabolites is 1/200 or less of the parent compound, whereas the β2-blocking activity is 1/10 or less.

Polymorphism

The enzymes responsible for landiolol metabolism are carboxylesterase in liver and pseudocholinesterase in plasma are considered not subjected to genetic polymorphism.

Dose proportionality and time dependency

In the study in Japanese subjects in which the volunteers received landiolol in two different infusion rates of 40 µg/kg and 80 µg/kg for 1 hour, dose proportionality was established in the Cmax and AUC as well (Murakami et al., 2005). The other studies with different doses are difficult to interpret with respect to the dose proportionality as the starting dose as well as the infusion rate differ in a non-proportional way. Landiolol and its main metabolite M1 do not show time dependent pharmacokinetics. The pharmacokinetic variables after two administrations of the same dose yield comparative pharmacokinetic variables. The exposure to landiolol and its metabolite M1 was approximately dose proportional over the tested dose range.

Intra- and inter-individual variability

The inter-individual variability in the pharmacokinetic variables is about 15%-30%. An analysis for the intra-individual variability in the pharmacokinetics of landiolol was provided and was estimated to be about 18%. This variability is acceptable. Target population The pharmacokinetics of landiolol and its main metabolite M1 was not changed in Japanese and Caucasian patients compared with healthy subjects. The effect of reduced cardiac output on the pharmacokinetics of landiolol was modelled with the PBPK model and the changes were considered of no clinical significance.

Special populations

Renal impairment

The use of Landiolol has not been evaluated in patients with renal impairment. The lack of clinical data in patients with renal impairment can be accepted. The impact of renal impairment on the pharmacokinetics is expected to be limited as landiolol is rapidly metabolised, only 10% of the dose is excreted by urine. Despite the fact that the metabolites are mainly excreted in urine the clinical impact of renal impairment on the metabolites is also expected to be limited as the metabolites are both inactive.

Hepatic impairment

The impact of liver function on the pharmacokinetics of landiolol was investigated in six

patients with mild to moderate hepatic impairment and six healthy volunteers blood concentrations of landiolol were significantly higher in patients with hepatic impairment (increase in geometric mean Cmax, Css and AUC0-∞ values in patients compared to healthy volunteers: +42%, +35% and +44%, respectively), but $t_{1/2}$ was not different from healthy adults. The PBPK model predicted the influence of hepatic impairment on the pharmacokinetics of landiolol. From the simulation, the effect of hepatic impairment was expected to be only marginal and unlikely to affect the safety and efficacy profile of landiolol significantly. The effect of severe hepatic impairment has not been evaluated.

Gender
Across studies gender differences were small; after administration of different doses landiolol exposure in females and males is comparable.

Age
Landiolol has been tested in elderly patients. However, limited PK data were provided and available PK data are difficult to compare due to administration of different doses and dosing regimens.

Race
Differences between the Japanese and Caucasian population are small. The literature data from studies with Onoact in the Japanese population can be used for elucidation of the pharmacokinetics in the Caucasian population, especially as the dose will be titrated to the optimum effect.

Weight
As landiolol will be administered on weight base doses, the influence of weight is considered of no clinical significance.

Overall, the presented pharmacokinetic data in the special populations are limited. No data on renal impairment, severe hepatic impairment and limited data on moderate hepatic impairment and elderly patients are presented. As landiolol has been marketed as Onoact since 2002 and as Rapibloc since 2016, there is sufficient experience with landiolol and post marketing data may be available to fill the gaps. The MAH was asked to summarise available post marketing data on the special populations and update the SmPC when applicable. No new pharmacokinetic data appears to be available for landiolol in special populations. The SmPC can therefore not be updated.

<u>Interactions</u>

In vitro
Landiolol nor its metabolites M1 and M2 exhibited *in vitro* inhibitory activity against human cytochrome P450. No interaction studies investigating the involvement of P-glycoprotein (Pgp) or the renal uptake transporters OAT1, OAT3 or OCT2 have been performed. The lack of these *in vitro* studies has been sufficiently justified.

In vivo
No pharmacokinetic drug interaction studies were performed. This is acceptable as it is not

expected that the distribution and metabolism will be affected by other medicinal products. It was shown that heparinisation decreased the exposure of landiolol by 50%. It is not expected that landiolol will affect the pharmacokinetics of other drugs.
In conclusion, pharmacokinetics of landiolol have been investigated sufficiently in healthy volunteers and patients with cardiac arrhythmias and undergoing cardiovascular surgery.

IV.3 Pharmacodynamics

The MAH provided an adequate overview of the available pharmacodynamic data.

The MAH submitted the results of the PK/PD studies performed in support of the registration of Onoact in Japan. This included the results of three PK/PD studies performed in 97 healthy Japanese or Chinese subjects, one study on six Japanese subjects with hepatic impairment (versus six healthy patients), one study on 19 Japanese patients with cardiac arrhythmias and one study on 18 Japanese patients undergoing cardio-vascular surgery. Infusion of landiolol resulted in a rapid dose-dependent decrease in heart rate. Heart rate, controlled by Landiolol infusion, was not affected by administration of heparin.

The results of four studies sponsored by AOP Orphan Pharmaceuticals were also submitted and included PK/PD assessments of Landiolol, i.e. Onoact and landiolol lyophilisate 600 mg and landiolol concentrate 20 mg, in a Caucasian population.

In the AOP-sponsored clinical studies 64 subjects were treated with Landiolol, 28 subjects were treated with the comparator Onoact and 42 subjects were treated with the comparator Brevibloc (esmolol). The AOP-sponsored studies submitted by the MAH showed infusion of landiolol resulted in a significant decrease in heart rate in healthy patients with a Caucasian background and in Caucasian patients with tachycardic AF or AFl.

In study LDLL600.201 a switch phase to oral therapy was started 180 minutes after Landiolol continuous infusion started. This was done by administering an oral beta blocker at 180 minutes and reducing the dose of the infusion by 50 % after 10 minutes and terminating the infusion after further 20 minutes at 210 min. As mentioned by the MAH the dosage of oral beta-blocker was not specified by protocol. In study LDLL600.201, only eight patients (8/20, 40.0%) were treated with bisoprolol, one patient (1/20, 5.0%) with nebivolol and one patient (1/20, 5.0%) with amiodarone. This does not provide sufficient justification to deviate from the currently approved text for Rapibloc (NL/H/3368/001). No new additional argumentation has been provided by the MAH in the current round. The MAH noted that if the proposed text is unacceptable, the MAH agrees to follow the currently approved text for Rapibloc (NL/H/3368/001). Issue is resolved if the MAH indeed follows the currently approved text for Rapibloc.

In the development program of Onoact, three dose-finding studies were conducted in Japanese subjects. The key findings of these studies were submitted for the current application. One study was performed in patients with paroxysmal atrial fibrillation/flutter or paroxysmal supraventricular tachycardia (Kato et al., 1997a), one in patients with perioperative tachyarrhythmia (Yoshiya et al., 2000) and one in patients with persisting postoperative supraventricular tachyarrhythmia (Taenaka & Kikawa, 2013a). All three studies

showed a dose dependent reduction of heart rate after landiolol infusion as expected.

The proposed interactions in section 4.5 of the SmPC are acceptable and in alignment with the current available literature and the registered SmPC of Rapibloc (NL/H/3368/001).

No studies were performed comparing the Caucasian to the Japanese subjects, however similar effects on heart rate and blood pressure were seen in healthy Caucasian subjects compared to Japanese subjects. Heart rates decreased shortly after the start of infusion with landiolol, remained lowered throughout the infusion period and returned to pre-administration values after discontinuation. A PBPK modelling was performed comparing the Japanese and Caucasian population. It is agreed with the MAH that based on the PBPK modelling the differences between the Japanese and Caucasian population seem small. Besides, the landiolol dose is titrated depending on patient characteristics (e.g. weight) and the clinical settings (e.g. the need for rapid onset of heartrate lowering effect) in a well-controlled clinical setting which will minimalised the risk of overdosing or a dose which is too low. Moreover, Landiolol lyophilisate 300 mg and Landiolol concentrate 20 mg are on the market in Europe since 2016. The proposed posology in the current application is in accordance with the Landiolol products registered.

Results for the two ongoing studies are still pending (a paediatric study and a study in patients with septic shock and associated tachycardia) and should be submitted when results become available.

Note: at the time of writing this PAR, the ongoing studies had been completed and submitted (see the note on page 16).

IV.4 Clinical efficacy

The MAH submitted 19 clinical studies with Onoact which were identified via a literature search, and one AOP-sponsored patient study with Landiolol lyophilisate 600 mg (Study LDLL600.201).

Onoact studies

In the 19 identified Onoact studies, a total of 1192 patients with SVT were treated with Landiolol. Open label studies and randomised controlled trials were considered, eight studies were placebo-controlled. Patients were treated with Landiolol in a peri-operative (i.e. preoperative + intraoperative), post-operative, and non-surgical setting. Most patients included in studies examining the peri- or post-operative setting had an elevated HR due to sinus tachycardia at baseline. Most patients included in studies examining the non-surgical setting had an elevated HR due to AF at baseline. Although demographic and baseline characteristics of the patient populations differed between studies, landiolol resulted in a reduction of HR in all studies. The submitted studies compared the effect on HR at baseline to 11 minutes up to 2 hours after landiolol administration, or examined the effect on HR comparing landiolol to placebo. The MAH submitted a meta-analyses of the efficacy data from these 19 Onoact studies. The following endpoints were considered in the meta-analyses:

- *Moderate improvement in HR reduction or better (HR reduction of ≥20% from baseline).* Studies were published between 1997 and 2014. Eight studies of patients treated in the peri- and post-operative settings were included, of these four studies were placebo controlled. Four studies in the non-surgical setting were included. The effect of Landiolol was measured at completion of effective dose level (11 minutes) up to 2 hours post dose. It is agreed with the MAH that Landiolol resulted in a moderate improvement in HR reduction in all studies. A dose dependent effect was seen between 10 and 40 µg/kg/min in the dose-finding studies published by Taenaka and Kikawa 2013b and Yoshiya et al., 2000. In the dose-finding study by Kato et al., 1997a using doses between 20 and 80 µg/kg/min, similar efficacy was observed for the two higher doses 40 and 80 µg/kg/min.
- *Substantial improvement in HR reduction (HR reduction of ≥30% from baseline).* The definition of substantial improvement was not uniform across studies. Studies were published between 1997 and 2014. Six studies of patients treated in the peri- and post-operative settings were included this analyses, of these 2 studies were placebo controlled and 1 study compared landiolol treatment to diltiazem treatment. Two studies in the non-surgical setting were included. The proportion of patients with substantial improvement in HR/ restoration of sinus rhythm ranged from 13.6% to 66.7% with the landiolol H dose category in the surgical setting studies. In the non-surgical setting, landiolol was administered to patients with heart failure and AF at low doses, the results on HR varied from a very minor effect on sinus rhythm to high proportion of patients with conversion to sinus rhythm. Landiolol was better than placebo in substantial improvement in HR reduction/ restoration of sinus rhythm in the 2 placebo controlled studies. A dose dependent effect was not seen across studies.
- *Change in HR from baseline.* The change in HR from baseline was assessed in 11 studies, in 9 studies patients were treated within the H dose category landiolol (125 µg/kg for 1 min, followed by 40 µg/kg/min). In the majority of studies, H dose landiolol was administered over a period of 11 minutes. For the peri-and post-operative studies, the mean change in HR from baseline ranged from -18.9% (11 min) to -34.9% (11 min) for the high dose category landiolol (125 µg/kg for 1 min, followed by 40 µg/kg/min). For the non-surgical studies, the mean change in HR from baseline ranged from -8.4% at 11 min to -20.3% at 11 min. In the Xiao et al., 2015 study (which used a 1+4 min administration regimen), the assessment was made at 5 min post-dose; however, reductions from baseline at 5 min were similar than in the other studies using the 11 min timepoint.

Study LDLL600.201. Study LDLL600.201 examined the pharmacodynamics, pharmacokinetics, tolerability and safety of Landiolol in Caucasian patients with tachycardic atrial fibrillation (AF) or atrial flutter (AFL) treated with a bolus + maintenance dosing scheme (bolus infusion of 100 µg/kg/min Landiolol for one minute, followed by continuous i.v. infusion of 40 µg/kg/min) or the maintenance only (continuous i.v. infusion of 40 µg/kg/min Landiolol) dosing scheme. The frequency of patients with successful HR control achieved and maintained during the first 16 min after continuous Landiolol infusion start (primary endpoint) was 50% for the overall analysis set (60.0% and 40.0% in the maintenance only dosing scheme and the bolus + maintenance dosing scheme, respectively). For patients with HR control in the maintenance only dosing scheme the median time to successful HR control was 12.0 min (95% CI [8.0, 16.0],

based on N=9). If successful HR control was not achieved after 16 min continuous infusion, the dose was increased to 80 µg/kg/min.
The median time to successful HR control was 8.0 minutes (95% CI [4.0, 14.0], based on N=4) for the patients who received a bolus infusion of 100 µg/kg/min Landiolol for one minute, followed by continuous i.v. infusion of 40 µg/kg/min.

Dosing recommendations
The MAH proposes to start with an infusion rate of 10 - 40 micrograms/kg/min which is considered acceptable. This dose is in alignment with the results from two dose-finding studies in which dose dependency was observed between 10 and 40 µg/kg/min (Taenaka and Kikawa, 2013b and Yoshiya et al., 2000). In the dose-finding study by Kato et al., 1997a doses between 20 and 80 µg/kg/min were studied, similar efficacy was observed for the two higher doses 40 and 80 µg/kg/min.

If rapid onset of the heartrate lowering effect is desired, an optional loading dose of 100 micrograms/kg/min for 1 min is suggested, followed by continuous intravenous infusion of 10 - 40 micrograms/kg/min. Although in the majority of Onact studies a bolus + maintenance dose of 125/40 µg/kg/min was administered, this optional loading dose is in alignment with the bolus dose administrated in study LDLL600.201.

For patients with LV dysfunction, landiolol lyophilisate 300 mg is proposed to be administered at low doses, starting from 1 µg/kg/min up to 10 µg/kg/min, and titrated to effect based on HR and blood pressure. Besides, landiolol lyophilisate 300 mg and landiolol concentrate 20 mg are on the market in Europe since 2016 and the proposed posology in the current application is in accordance with the landiolol products registered (Rapibloc 300 mg poeder voor oplossing voor infusie, NL/H/3368/001).

IV.5 Clinical safety

Safety information on landiolol is mainly obtained from 38 clinical studies with Onoact (identified via a literature search), and from four AOP-sponsored clinical studies with landiolol lyophilisate or Landiolol concentrate.

The general AE (Adverse Event) profile appears to be in line with what would be expected for a short-acting selective beta-blocker. Comparing landiolol with an active comparator in the Onact studies did not raise new safety concerns. The most common adverse events related to landiolol reported in the Onact studes were hypotension and bradycardia as expected.

Studying AE with landiolol by dose category did not suggested dose dependent safety concerns.

Adverse events in patients with left ventricular dysfunction were examined in 145 subjects in two studies (Adachi et al. 2014, Nagai et al. 2013). The SmPC recommends lower doses starting from 1 microgram/kg /min up to 10 micrograms/kg /min in patients with impaired left ventricular function (LVEF <40%, CI <2.5 L/min/m2, NYHA 3-4). Besides, the SmPC mentions that further dose increases may be considered under close hemodynamic monitoring if required and tolerated by the patient´s cardiovascular status.

In conclusion, Landiolol is only administered in a well-controlled medical setting, discontinuation due to adverse events is mainly due to decreased blood pressure, hypotension and bradycardia which are all known side effects of beta-blockers. Recovery of heart rate and blood pressure to pre-administration values occurred within 30 minutes of discontinuation of landiolol. The reported AEs are in alignment with the proposed SmPC.

IV.6 Summary Pharmacovigilance system

The MAH has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

IV.7 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Landiolol Hydrochloride Orpha-Devel 300 mg. At the time of approval, the most recent version of the RMP was version vOD1.0, signed 6 November 2023.

Table 4. Summary table of safety concerns as approved in RMP

Important identified risks	• Severe hypotension • Severe bradycardia • Cardiac arrest
Important potential risks	None
Missing information	• Use in paediatric population (<18 years old) • Use in pregnancy and breastfeeding.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.8 Discussion on the clinical aspects

The application is based on published data on the pharmacology, efficacy and safety of Onoact (a lyophilised 50 mg formulation of landiolol authorised in Japan in 2002). In addition, the MAH submitted clinical studies with Onoact/ landiolol, landiolol lyophilisate or landiolol concentrate and one physiology-based pharmacokinetic (PBPK) modelling study. In 2016 landiolol lyophilisate 300 mg was approved via the decentralised procedure in various European countries (trade names: Rapibloc, Raploc, Landiobloc, Runrapiq) with the same indications as targeted in the current Marketing Authorisation Application.
Risk management is adequately addressed. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Rapibloc 300 mg / 600 mg powder for solution for infusion (NL/H/3368/001-003/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Landiolol Hydrochloride Orpha-Devel 300 mg powder for solution for infusion has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. This application is partially based on published data on the pharmacology, efficacy and safety of Onoact. Bridging of the data in the literature to the current product has been adequately performed.

Based on the review of the data on quality, safety and efficacy, the Benefit/Risk ratio of Landiolol Hydrochloride Orpha-Devel is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between the member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the benefit-risk balance for Landiolol Hydrochloride Orpha-Devel 300 mg powder for solution for infusion, is positive and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 November 2023.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5509/001/ IB/001	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier: - Re-test period/storage period. - Extension or introduction of a re-test period/storage period supported by real time data.	No	21-3-2024	Approved	N.A.
*NL/H/5509/001/ II/002	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. - To update the clinical information in the SmPC to reflect observations made in a clinical study newly published literature.	Yes	7-11-2024	Approved	N.A.
NL/H/5509/001/ IB/003	Change in the shelf-life or storage conditions of the finished product: - Extension of the shelf-life of the finished product. - As packaged for sale (supported by real time data).	Yes	23-7-2025	Approved	N.A.
NL/H/5509/001/ IA/005	Change in test procedure for the finished product: - Minor changes to an approved test procedure.	No	10-11-2025	Approved	N.A.

NL/H/5509/001/ IB/006	Change in the shelf-life or storage conditions of the finished product: - Change in storage conditions of the finished product or the diluted/reconstituted product.	Yes	27-3-2026	Approved	N.A.
NL/H/5509/001/ IA/007	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance: - Up to 10-fold increase compared to the originally approved batch size.	No	13-2-2026	Approved	N.A.

* See Annex 1, Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet (Type II variation NL/H/5509/001/II/002).

Annex I- Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet (Type II variation NL/H/5509/001/II/002)

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the Medicines Evaluation Board of the Netherlands (MEB) has accepted the variation for changes in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

As requested, the MAH submitted the revised Summary of Product Characteristics, Labelling or Package Leaflet including the approved changes of this variation.

II. EXECUTIVE SUMMARY

II.1. Scope of the variation

The variation is to update the clinical information in the SmPC to reflect observations made in a clinical study.

The updates have been made throughout the SmPC's text (i.e., posology, warnings, undesirable effects, pharmacokinetic properties). The details of the changes in the SmPC are well described in the present-proposed table attached as Annex - LDLL 1.2 SmPC Present and proposed table V026 to this application form.

III. SCIENTIFIC DISCUSSION

III.1. Quality aspects

N/A

III.2. Non clinical aspects

N/A

III.3. Clinical aspects

III.3.1. Clinical pharmacology

In section 5.2 of the SmPC, the MAH suggests to change the statement regarding renal impairment "The pharmacokinetics in patients with renal impairment has not been evaluated." into "The pharmacokinetics in patients with mild or moderate renal impairment has not been evaluated.

The pharmacokinetic characteristics of landiolol were studied in patients (n=7) with septic shock undergoing renal replacement therapy. The contribution of dialytic clearance to the total clearance of landiolol was approximately 2% and considered negligible. For the landiolol metabolite M1, the contribution of dialytic clearance to total clearance was approximately 30%. No accumulation of landiolol and its metabolite M1 was observed over the study period of 8 hours. The results of the clinical study indicate that no special precautions are required when administering landiolol to patients undergoing renal replacement therapy."

Methods
A study was submitted (LANDI-SEP) in which the pharmacokinetics (PK) and dialytic clearance of landiolol and its metabolite M1 were investigated in patients with septic shock and persistent tachycardia/tachyarrhythmia undergoing renal replacement therapy (RRT). A total of 7 patients were enrolled (4 males and 3 females, aged 37 – 79 years, BMI 21 – 39 kg/m2). Patients were treated with Landiolol lyophilisate 300 mg (LDLL300) by intravenous infusion. The dose was first titrated at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min in order to obtain a target heart rate of 80-94 bpm. Thereafter, LDLL300 was infused continuously to maintain a heart rate of 80-94 bpm. After the titration period (at the start of the PK sub-study), blood samples were collected at 0 h, 2 h, 4 h and 8 h. One of the patients stopped after 2 hours infusion (patient S16-48). At the time points of blood sample collection, also a dialyser inlet sample and a dialyser outlet sample were collected. PK parameters were AUC and total clearance (body clearance + dialytic clearance). Dialytic clearance was calculated using the A-V (arterio-venous) difference method. Descriptive statistics were performed. Statistical analyses were performed using SAS, version 9.4. Dialytic clearance was assessed using the formula ClD = (Cin-Cout)×QB/Cin where Cin = Concentration at inlet port; Cout = concentration at outlet port; QB = blood flow rate; ClD = Dialytic clearance. AUCs for 2 h intervals were calculated by the linear trapezoidal method. The following calculations were performed to evaluate a potential accumulation of Landiolol and Landiolol M1:

- Ratio AUC(2-4h)/AUC(0-2h)
- Ratio 0.5*AUC(4-8h)/AUC(2-4h)
- Ratio 0.5*AUC(4-8h)/AUC(0-2h)

Results
<u>Clearance</u>
The mean dialytic clearance for Landiolol overall (without patient S16-48) was 39.33 (±26.51) mL/min, with a minimum of 18.2 mL/min and a maximum of 81.4 mL/min. The mean dialytic clearance for metabolite M1 overall (without patient S16-48) was 42.30 (± 11.56) mL/min, with a minimum of 19.7 mL/min and a maximum of 53.2 mL/min. Dialytic, body and total clearance of landiolol and M1 are shown in table 1 and table 2.

Table 4 Dialytic, body and total clearance for landiolol (without patient S16-48)

Subject ID	Dialytic clearance Cl_D (±SD) (mL/min)	Total dose D_L (mg)	Body clearance Cl_B (mL/min)	Body clearance Cl_B (mL/min/kg)	Total clearance Cl_T (mL/min)	Total clearance Cl_T (mL/min/kg)	Ratio Cl_D/Cl_T (%)
S16-37	19.61 (±8.474)	60.0	2443.2	40.7	2462.8	41.0	0.8
S16-44	18.23 (±7.483)	136.0	1437.4	20.5	1455.7	20.8	1.3
S18-23	28.44 (±10.731)	947.2	1941.9	27.7	1970.4	28.1	1.4
S18-25	81.36 (±22.134)	222.7	1621.8	20.3	1703.2	21.3	4.8
S18-27	63.50 (±14.134)	540.5	1648.9	18.3	1712.4	19.0	3.7
S18-30	24.84 (±15.368)	1011.7	1425.6	17.8	1450.4	18.1	1.7
Mean (±SD)	39.33 (±26.508)	486.35 (±416.014)	1753.15 (±386.491)	24.24 (±8.827)	1792.48 (±381.001)	24.74 (±8.733)	2.28 (±1.585)
Median	26.64	381.59	1635.38	20.40	1707.81	21.04	1.58
Q1 / Q3	19.61/63.50	136.01/947.18	1437.43/1941.92	18.32/27.74	1455.66/1970.36	19.03/28.15	1.25/3.71
Min / Max	18.2/81.4	60.0/1011.7	1425.6/2443.2	17.8/40.7	1450.4/2462.8	18.1/41.0	0.8/4.8

Table 5 Dialytic, body and total clearance for main metabolite M1 (without patient S16-48)

Subject ID	Dialytic clearance Cl_D (±SD) (mL/min)	Total dose D_{M1} (mg)	Body clearance Cl_B (mL/min)	Body clearance Cl_B (mL/min/kg)	Total clearance Cl_T (mL/min)	Total clearance Cl_T (mL/min/kg)	Ratio Cl_D/Cl_T (%)
S16-37	45.28 (±12.902)	46.6	31.2	0.5	76.5	1.3	59.2
S16-44	46.83 (±10.944)	105.5	90.6	1.3	137.5	2.0	34.1
S18-23	44.91 (±14.517)	735.0	191.5	2.7	236.4	3.4	19.0
S18-25	43.93 (±12.448)	172.8	163.6	2.0	207.5	2.6	21.2
S18-27	53.17 (±6.646)	419.5	116.0	1.3	169.1	1.9	31.4
S18-30	19.69 (±4.184)	785.1	156.0	2.0	175.7	2.2	11.2
Mean (±SD)	42.30 (±11.559)	377.42 (±322.842)	124.82 (±58.194)	1.64 (±0.769)	167.12 (±55.865)	2.21 (±0.715)	29.35 (±16.855)
Median	45.09	296.13	135.99	1.62	172.42	2.08	26.30
Q1 / Q3	43.93/46.83	105.55/735.05	90.63/163.58	1.29/2.04	137.46/207.51	1.88/2.59	19.00/34.07
Min / Max	19.7/53.2	46.6/785.1	31.2/191.5	0.5/2.7	76.5/236.4	1.3/3.4	11.2/59.2

AUC

The mean total AUC (0-8 h) for Landiolol (without patient S16-48) was 296.95 (± 263.94) µg/min/mL, with a minimum of 24.6 µg/min/mL and a maximum of 709.7 µg/min/mL. The

mean total AUC for Landiolol M1 (without patient S16-48) was 2700.03 (± 1679.02) µg/min/mL, with a minimum of 1056.3 µg/min/mL and a maximum of 5032.3 µg/min/mL.

The assessment of potential accumulation is shown in table 3. The MAH concludes that the comparison of AUCs in these intervals for these patients did not reveal any accumulation for landiolol and M1.

Table 6 Estimation of accumulation of landiolol and M1 over 8 hours (data excluding patient S16-48) (mean ± SD, range)

	Landiolol	**M1**
AUC(2-4h)/AUC(0-2h)	121.04 ± 33.75% (84.0 – 172.7%)	110.38 ± 10.23% (92.0 - 121.0 %)
0.5*AUC(4-8h)/AUC(2-4h)	116.43 ± 27.93% (89.3 - 162.6 %)	111.53 ± 22.91% (84.3 - 141.2 %)
0.5*AUC(4-8h)/AUC(0-2h)	138.55 ± 40.44% (92.2 - 195.4 %)	124.22 ± 33.46% (89.8 - 162.5 %)

Assessor's comment:
The study shows no significant accumulation in these patients over 8 hours. The proposed text has already been accepted for Rapibloc 300 mg powder for solution for infusion and is therefore agreed.

III.3.2 Clinical efficacy

Main study
The proposed changes to the SmPC are based on the data acquired in the LANDI-SEP trial. LANDI-SEP was a phase IV, multicentre, prospective, randomised, open-label, controlled study on Landiolol in patients with septic shock resident in an Intensive Care Unit.

Introduction/rationale:
In the early phase of septic shock, overwhelming inflammation leads to vasodilation and capillary leakage, which decreases cardiac output due to both absolute and relative hypovolemia (Bhagat, et al. 1999; Marx, et al. 2000; Parrillo 1993). These alterations trigger massive sympathetic activation in an attempt to maintain vital organ perfusion. Tachycardia and vasoconstriction are the hallmarks of this activation and compensate for systemic vasodilatation (Rhodes, et al. 2017). In the very early phase of the septic insult, tachycardia is the main compensatory mechanism to maintain cardiac output, despite the reduction of preload. Accordingly, current sepsis guidelines recommend intravascular fluid administration as the first step to counteract hypotension (Dunser and Hasibeder 2009; Rhodes, et al. 2017). Compensatory tachycardia implies preserved baroreceptor and chemoreceptor activity, thus the majority of patients with sepsis rapidly respond to volume administration with a reduction of tachycardia. However, some patients with sepsis continue to have an elevated heart rate (HR) despite adequate fluid resuscitation. This elevated HR reflects sympathetic overstimulation resulting from dysregulation of the autonomic nervous system (Dunser and Hasibeder 2009; Leibovici, et al. 2007; Morelli, et al. 2013b; Rudiger and Singer 2013; Sander, et al. 2005; Schmidt, et al. 2005; Schmittinger, et al. 2012; Werdan, et al. 2009) in addition to

the effect of exogenous catecholamines (Schmittinger, et al. 2012). Hence, in the septic patient, tachycardia which does not respond to adequate volume resuscitation, indicates an altered chronotropic response rather than hypovolemia or demand for supranormal oxygen delivery and thus can be considered as an early manifestation of septic myocardial dysfunction.

Since tachycardia is associated with poor outcome even in septic shock, a reduction in HR should be considered as one of the therapeutic targets to improve patient outcome. Elevated HR has been associated with a poor outcome, but it is unclear whether it is a surrogate of disease severity, or whether it plays a pathophysiological role that could be treated to improve patient outcomes (Grander, et al. 2013; Hayase, et al. 2016; Hoke, et al. 2012; Vellinga, et al. 2015).

In septic shock patients a HR threshold of 95 bpm has been reported as an optimally predictive cut-off value to differentiate between survivors and non-survivors (Kumar, et al. 2008). Morelli et al. (Morelli, et al. 2013a; Morelli, et al. 2013b) demonstrated that a HR range between 80-94 bpm was a sufficient compromise between improving cardiac performance and preserving systemic haemodynamics. Collectively, findings suggest that adopting a predefined HR range between 80-94 bpm, or a HR reduction of 20-30 percent, does not negatively affect systemic haemodynamics and organ perfusion in rates above 110 bpm (Balik, et al. 2012; Gore and Wolfe 2006; Kumar, et al. 2008; Morelli, et al. 2013a; Morelli, et al. 2013b; Schmittinger, et al. 2008). Beta-blockers are potential candidates to control HR and numerous animal models provide a rationale for their use during sepsis (Aboab, et al. 2011; Ackland, et al. 2010; Calzavacca, et al. 2014; Du, et al. 2017; Hagiwara, et al. 2009; Kimmoun, et al. 2015; Suzuki, et al. 2005; Wei, et al. 2016). Despite concerns of hemodynamic decompensation, recent clinical studies using esmolol in patients with sepsis (Balik, et al. 2012; Chen, et al. 2013; Du, et al. 2016; Morelli, et al. 2013a; Morelli, et al. 2013b; Shang, et al. 2016; Tao, et al. 2015; Wang, et al. 2017; Wang, et al. 2015; Xinqiang, et al. 2015; Yang, et al. 2014) suggest that control of HR can be safely achieved with beta1-selective beta-blockers. These studies reported a decrease in HR with limited reduction of cardiac output, improved stroke volume and lactate levels, and stabilisation or improvement of organ dysfunction (Morelli, et al. 2013b; Shang, et al. 2016; Tao, et al. 2015; Wang, et al. 2017). Furthermore, the combined use of beta-blockers and vasopressors appears to be safe and does not appear to increase the need for vasopressor support or impair microcirculation (Balik, et al. 2012; Du, et al. 2016; Morelli, et al. 2013a).

Hence, beta-blockers such as Landiolol, appear to be the most appropriate drugs for treating noncompensatory tachycardia in septic shock. However, the clinical studies performed to date were conducted in single centers with relatively small sample sizes and only one study included a Caucasian population. Therefore, this multicentre, prospective, controlled LANDI-SEP study was undertaken to demonstrate that the administration of the ultrashort-acting beta-blocker Landiolol (LDLL300) in patients with septic shock and persistent tachycardia (HR ≥ 95 beats per minutes [bpm]) is effective in reducing and maintaining HR, without increasing vasopressor requirements (Unger, et al. 2018).

The aim of this study was to demonstrate, in a multicentre setting, that administration of an injectable short half-life beta-blocker (LDLL300) in patients with septic shock and persistent

tachycardia/ tachyarrhythmia is effective in reducing and maintaining heart rate without increase in vasopressor requirements.

Methods

This was a multicentre, randomised, controlled, open-label phase IV trial in patients with septic shock and persistent tachycardia/tachyarrhythmia (HR ≥95 bpm) treated with LDLL300 in addition to standard treatment versus standard treatment alone (i.e., no treatment with betablockers). Patients with septic shock resident in the Intensive care unit (ICU), who after having completed the haemodynamic optimisation phase (at least 12 hours, but a maximum of 36 hours after resuscitation according to SSCG 2016 guidelines), still had tachycardia and/or tachyarrhythmia with HR ≥95 bpm were assessed by applying the selection (inclusion/exclusion) criteria.

According to the Surviving Sepsis Campaign Guidelines (SSCG), septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (Rhodes, et al. 2017). Due to the high sympathetic stress consequent to sepsis-induced myocardial depression, it has been observed that patients with septic shock may often remain tachycardic, even after having excluded the common causes of tachycardia and supplied a proper therapy aimed to reverse the hypovolemia and the elevated compensatory heart rate. The use of intravenous beta-blocker in tachycardic septic patients has shown haemodynamic advantages (i.e. maintenance of heart rate within an acceptable range of 80 – 94 bpm, increase of stroke volume, maintenance of appropriate mean arterial pressure) compared to standard treatment (no treatment with beta-blockers). This was also associated with a reduction in norepinephrine requirements as well as an increase in cardiovascular performance and, eventually, an improvement in 28-day survival (Morelli, et al. 2013b).

Objectives

The primary objective was to compare the rate of patients with heart rate response (80-94 bpm) and maintenance thereof without increase in vasopressor requirements in the first 24 hours after treatment start in a septic shock population with persistent tachycardia (≥95 bpm), randomised to either standard treatment and continuous LDLL300 infusion (group L), or standard treatment only (group C).

Secondary objective was to further assess efficacy and safety in the two treatment groups.

The rationale for the chosen primary endpoint “Heart rate response (80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours” is to show that HR may be reduced in patients with septic shock and non-compensatory tachycardia without compromising haemodynamic stability. The secondary endpoints serve to explore the potential benefits of reducing HR in the study population in regard to mortality and ICU/hospital stay duration and to further assess the efficacy and safety of LDLL300. Patients in the control group (group C) received standard treatment according to the SSCG 2016 (Rhodes, et al. 2017) for the entire study period. This treatment was not specifically targeted to HR control.

Endpoints

Primary efficacy endpoint:

Heart rate response (i.e. HR = 80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start.

Secondary efficacy endpoints:

- Change in vasopressor requirements over the study period (dose and duration)
- Heart rate response (i.e. HR = 80-94 bpm) during the first 24 hours after treatment start
- 28-day mortality (all cause)
- ICU mortality (all cause)
- Duration of ICU stay (survivors/non-survivors)
- Duration of hospital stay (survivors/non-survivors)
- Daily inotropic requirements (as long as the patient is treated with vasopressors).

Safety endpoints (safety evaluation):

- Incidence of Adverse Events (AE)
- Incidence of Serious Adverse Events (SAE)
- Incidence rate of bradycardic episodes requiring intervention

Treatments:

The sponsor was to provide the sites with supplies of LDLL300 as study medication (IMP) to be administered to patients during the trial. Treatment during the trial was assigned as follows:

Group L:

Patients of group L received standard treatment according to SSCG 2016 (Rhodes, et al. 2017) and treatment with LDLL300 for the duration of vasopressor treatment according to the following dosing scheme.

Titration phase (first 24 hours after treatment start):

- Administration of the study drug had to start within 2 hours after randomisation
- Starting dose 1 µg/kg/min
- Dose progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min with a minimum dose interval of 20 minutes to a maximum dose of 40 µg/kg/min in order to obtain a target HR of 80-94 bpm. LDLL300 had to be infused then at any dose (1 µg/kg/min to 40 µg/kg/min) to maintain target HR.

Maintenance Phase I, II:

- LDLL300 had to be infused continuously at any doses (between 1 µg/kg/min and 40 µg/kg/min) to maintain a HR of 80–94 bpm for the duration of vasopressor infusion. LDLL300 infusion had to be terminated if one of the following events occurred:
- Death, a serious adverse event attributable to the study drug infusion (if deemed necessary by the Investigator), vasopressor infusion discontinuation, the patient's discharge from ICU, or day 28.

Group C:

Patients in group C received standard treatment according to SSCG 2016 (Rhodes, et al. 2017), which was not specifically targeted to HR control. Patients in group C who had prior

vasopressor infusion discontinuation and were in need of beta-blocker therapy, but no alternative treatment was deemed appropriate, were to be withdrawn from the study.

Selection of doses in the study

The chosen dosages are within the range of doses used in previous clinical trials. The starting dose of 1 µg/kg/min could be progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min with a minimum dose interval of 20 minutes in order to obtain and maintain a HR of 80-94 bpm. The risk of overdose was considered low, as each patient was closely monitored and the dosage of LDLL300 was titrated and immediately adjusted, if needed.

Measurements

Hemodynamic data [HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP)] were documented hourly in the titration phase and every 12 hours thereafter until end of treatment. Rate of vasopressor and inotrope infusion was recorded at every dose change.

Statistical analysis

Sample size justification

Assuming that the primary endpoint reached 60% of patients in group L vs. 40% of patients in group C, a total number of 194 patients (97 patients in each treatment group) would provide 80% power to demonstrate a statistically significant difference between treatment groups using a Chi-square test at a level of significance alpha=5%.

The primary endpoint was measured at 24 hours after treatment start. Patients who died during the first 24 hours without reaching the primary endpoint were included in the analysis (with the outcome that the primary endpoint was not reached); therefore, no drop-outs from the primary analysis were assumed. Taking the application of block randomisation stratified in two stratification groups into account, the total number of patients to be randomised was set to 200 (100 patients in each treatment group).

The statistical analysis was performed in accordance with the latest approved study protocol, International Conference on Harmonisation Topic E9, Statistical Principles for Clinical Trials and the Statistical Analysis Plan (SAP) finalised and approved by the Sponsor and the study statistician before database lock.

Efficacy analysis

Primary efficacy analysis Absolute and relative frequencies of patients who achieved the primary endpoint were calculated. The comparison of treatment groups was conducted using a weighted Cochran-Mantel-Haenszel (according to SAS terminology) framework with two stratification factors (according to SAS terminology): the presence of atrial fibrillation and site. The hypothesis that group L is superior to group C in the proportion of patients who reached the primary endpoint was demonstrated if the lower limit of two-sided 95% Newcombe confidence interval of difference pL - pC was above zero, where pL and pC are percentages of patients who reached the primary endpoint in group L and group C, respectively. P-value based on the Cochran-Mantel-Haenszel Statistics for testing of statistical significance of association between treatment group and outcome after adjustment for stratification factors was presented together with the confidence intervals. The analysis was primarily performed using the FAS. To conclude, the hypotheses needed to be demonstrated using the FAS and

supported by analysis using the PPS. Secondary efficacy analysis continuous and binary variables measured at more time-points were analysed as longitudinal data by linear, logistic, or log-binomial regression models with repeated measures. For continuous data, a Mixed Model with Repeated Measures (MMRM) implemented in PROC MIXED in SAS was used. The calculation of (ordinal) logistic regression was performed using method Generalised Estimating Equations (GEE) implemented in PROC GENMOD in SAS. Comparison of treatment groups in binary endpoints using relative risk reduction calculated by log-binomial regression model was preferred. The time-to-event data was analysed using Kaplan-Meier curve and log-rank test or Wilcoxon test (the choice was based on the check of assumptions); the Cox proportional regression hazard model was also performed if assumptions were fulfilled. Covariates used in the models were (but were not limited to) treatment, visit, stratification group (real value), interaction treatment*visit, site/country and interaction site/country*treatment. The first choice was to use the effect of site and its interaction with treatment; when it was not possible because of the low number of patients in some of the sites, the country was used; if the model with country was also not suitable (especially for subgroups' analyses), this effect was not used. For continuous variables, the baseline value of the outcome variable was covariate as well. Distribution of data and feasibility check of planned analyses was performed before finalisation of the SAP and alternative statistical methods were defined, if assumptions of the planned methods used were not met (e.g. ln-transformation of data, non-parametric method, or other alternative). Change in vasopressor requirements over the study period was calculated as difference [dose at study treatment start] - [dose after study treatment start at defined time-point] and compared between treatment groups. Duration and dose of vasopressors was also compared between treatment groups.

Daily inotropic requirements were analysed using a similar manner; however, only the period when the patient was treated by vasopressors was taken into account. 28-day mortality and ICU mortality were analysed using the same methods as the primary endpoint. For the ICU mortality, the patients not discharged from ICU on day 28 are assumed to be survivors. Moreover, the survival time (difference between time of death and the treatment start) were analysed as time-to event data. Duration of ICU stay and duration of hospital stay in survivors was analysed as time-to-event data (using Kaplan-Meier curve, and using log-rank test or Wilcoxon test and/or proportional hazards regression model). SOFA score ranges from 0 (normal) to 24 (the worst degree of dysfunction/failure) and was planned to be analysed as a continuous variable. It was evaluated for the visits before the end of vasopressors treatment only. The values and changes from baseline were summarised by treatment groups for the patients still treated by vasopressors and compared by linear model for each visit separately. If there was no major violation of normal distribution, no transformation was needed Secondary exploratory analyses The heart rate and blood pressure (mean arterial pressure, systolic arterial pressure and diastolic blood pressure) were analysed during the titration phase (every hour) and maintenance phases (every 24h), before the end of vasopressors treatment only. The values, changes from baseline and relative changes from baseline were summarised by treatment groups for the patients still treated by vasopressors and compared by linear model for each visit separately. If there was no major violation of normal distribution, no transformation was needed.
Subgroup analysis by strata or analysis with adjustment for other covariates using log-binomial regression model was performed for exploratory purposes.

Safety analysis
Absolute and relative frequencies of patients with treatment emergent adverse events, count and incidence rate of events overall and by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) were calculated. The same descriptive statistics were calculated also for bradycardia episodes requiring intervention. The frequency tables of adverse events presented the following types of events separately: all treatment emergent events, serious adverse events (SAEs), events leading to death, events leading to study discontinuation and events leading to dose reduction. Further, frequency tables by relationship to study drug and by intensity were displayed.

Results
Planned: 200 patients.
Enrolled/ Randomised: 200 patients (99 patients in group L and 101 patients in group C).
Treated: 196 patients (98 patients in group L and 98 patients in group C).
Not Treated: 4 patients (1 patient in group L and 3 patients in group C).
Full Analysis Set (FAS): 196 patients (98 patients in group L and 98 patients in group C).
Per Protocol Set (PPS): 176 patients (87 patients in group L and 89 patients in group C).

A total of 200 patients with septic shock were enrolled in the study, at 20 sites in 7 countries in Europe. Of these, 196 randomised patients were treated in total, with 98 patients in each treatment group. The mean age was 64.4 (±12.50) years in group L and 65.2 (±15.06) years in group C, with ranges of 26-93 years and 23-88 years, respectively. A total of 35 (35.7%) patients were female in group L; in group C 43 (43.9%) patients were female. The majority of patients enrolled in the study (99.5%) were white. A total of 26 (26.5%) patients in group L and 24 (24.5%) patients in group C had atrial fibrillation. The treatment groups (FAS) were well balanced with no statistically significant differences detected between the treatment groups at screening (assessed by Wilcoxon, Fischer, or t-test).

Patients in group C received standard treatment according to SSCG 2016 (this treatment was not specifically targeted to HR control). Patients in group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor treatment. In the titration phase, which was the first 24 hours after treatment start, patients were administered LDLL300 at a starting dose of 1 µg/kg/min, with the dose progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min with a minimum dose interval of 20 minutes in order to obtain a target HR of 80-94 bpm. LDLL300 had to be infused then at any dose (1 µg/kg/min to 40 µg/kg/min) to maintain target HR.

In maintenance phase I (day 2 to day 4) and maintenance phase II (day 5 to day 28), LDLL300 had to be infused continuously to maintain a HR of 80–94 bpm for the duration of vasopressor infusion. The mean LDLL300 dose administered over the whole treatment period was 2955.84 (±5315.610) mg, with mean LDLL300 doses administered during the titration phase, maintenance phase I and maintenance phase II of 807.90 (±1059.193) mg, 2048.93 (±2736.315) mg and 4072.06 (±5170.502) mg respectively. The median LDLL300 dose over the whole treatment period was 786.86 (range 0.8 - 33252.0) mg. The median LDLL300 doses administered during the titration phase, maintenance phase I and maintenance phase II were 387.96 (range 0.8 -7140.0) mg, 897.95 (range 38.8 - 11037.2) mg and 1990.73 (range 3.4 - 20684.4) mg, respectively. The mean total daily duration of LDLL300 treatment (between the

start and the end of the treatment) was 2.803 (±3.3703) days. The mean daily infusion duration was 2.671 (±3.1644) days and the median daily infusion duration was 1.602 (Q1-Q3: 0.789 - 3.308) days, with a minimum of 0.01 and a maximum of 16.78 days.

Endpoints

Primary endpoint

The primary efficacy endpoint of the study was the heart rate response and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start. The results outlined below are for the FAS and were confirmed in the PPS.

• The primary response was achieved in 39/98 (39.8%) patients in group L, compared to 23/98 (23.5%) patients in group C, with a difference between the response rates of 16.5% (95% CI: 3.4% to 28.8%), indicating that a statistically significantly (p=0.0133) higher proportion of patients in group L were responders achieving the primary response (see table below).

Table 7. Analysis of the percentage of patients with the primary response (FAS)

Response	Group L	Group C	Overall	Difference between the response rate (95% CI)*	p-value**
Non-responder	59 (60.2%)	75 (76.5%)	134 (68.4%)		
Responder	39 (39.8%)	23 (23.5%)	62 (31.6%)	16.5% (3.4%, 28.8%)	0.0133

* Newcomb CI interval with the stratification factor presence of atrial fibrillation
** Cochran-Mantel-Haenszel test with the stratification factor presence of atrial fibrillation

The results of the primary endpoint in the FAS were confirmed in the PPS, see table below.

Table 8. Analysis of the percentage of patients with the primary response (PPS)

Response	Group L	Group C	Overall	Difference between the response rate (95% CI)*	p-value**
Non-responder	55 (63.2%)	69 (77.5%)	124 (70.5%)		
Responder	32 (36.8%)	20 (22.5%)	52 (29.5%)	14.4% (0.8%, 27.2%)	0.0375

* Newcomb CI interval with the stratification factor presence of atrial fibrillation
** Cochran-Mantel-Haenszel test with the stratification factor presence of atrial fibrillation

• With regard to the percentage of patients with the heart rate response (target heart rate reached, not necessarily maintained), 74/98 (75.5%) patients in group L were responders compared to 42/98 (42.9%) patients in group C, with a difference between the response rates of 33.0% (95% CI: 19.4%, 44.9%), indicating that a statistically significantly (p<.0001) higher proportion of patients in group L reached the target heart rate.

• With regard to the percentage of patients with the heart rate response (target heart rate reached and maintained), 57/98 (58.2%) patients in group L were responders compared to 29/98 (29.6%) patients in group C, with a difference between the response rates of 29.0%

(95% CI: 15.1% to 41.3%), indicating that a statistically significantly (p<.0001) higher proportion of patients in group L reached and maintained the target heart rate.
• In the majority of patients vasopressor requirements at hour 24 were equal, or lower than, at treatment start (defined as vasopressor responders), 56/98 (57.1%) patients in group L and 65/98 (66.3%) patients in group C were responders, with a difference between the vasopressors response rates of -9.2% (95% CI: -22% to 4.4%), which was not statistically significant (p=0.1877).
Overall, administration of the injectable short half-life beta-blocker Landiolol in patients with septic shock and persistent tachycardia/ tachyarrhythmia was effective in reducing and maintaining heart rate, with no increase in vasopressor requirements during the first 24 hours in a significantly higher proportion of patients in group L (p=0.0133) compared to group C, thus the primary endpoint of the study was met.

Secondary analysis
The duration of vasopressors administration in the study was similar for both treatment groups. For group L the mean vasopressor use was 5.64 (±7.162) days with a median of 2.95 (Q1-Q3: 1.08 - 5.91) days. For group C the mean vasopressor use was 5.08 (±5.195) days with a median of 3.44 (Q1-Q3: 1.33 - 7.09).
The mean duration of inotropic agents administered in the study was higher for group L at 3.95 (±3.777) days with a median of 2.18 (Q1-Q3: 1.08 – 5.23) days, compared to group C with a mean of 1.32 (±1.125) days with a median of 0.99 (Q1-Q3: 0.37 – 1.60) days.
The 28-day mortality was similar for both treatment groups. A total of 43/98 (43.9%) patients in group L and 39/97 (40.2%) patients in group C died during the 28-day course of the study, with a difference of 3.8% (95% CI: -9.9% to 17.3%), hence there was no significant difference (p=0.5954) in mortality rate between the treatment groups.
ICU mortality was also similar across treatment groups. A total of 43/98 (43.9%) patients in group L and 33/97 (34.0%) patients in group C died in the ICU during the study. The difference in ICU mortality between the treatment groups was 9.9% (95% CI: -3.8% to 23.0%), which was not statistically significant (p=0.1592).
The time of survival by treatment groups was analysed by Kaplan – Meier analyses with treatment groups compared by log-rank test (p=0.2945) and by Cox proportional hazards model (hazard ratio 1.35, 95% CI: 0.85 to 2.13, the difference between treatment groups was not statistically significant [p =0.1986]).
The duration of ICU stay for patients alive on day 28 was analysed by Kaplan – Meier analyses and treatment groups were compared by log-rank test (p=0.4501) and by Cox proportional hazards model ((hazard ratio 1.17, 95% CI: 0.70 to 1.94, the difference between treatment groups was not statistically significant [p=0.5506]).
The duration of hospital stay for patients alive on day 28 did not statistically significantly differ between the treatment groups [p (Chi-Square Cox proportional hazard model) = 0.4965].

Haemodynamic parameters
There was a significant decrease (p<.0001) in heart rate in patients in group L at one hour after treatment with LDLL300. The mean change from baseline was -14.23 (±17.463) bpm for group L and -1.59 (±9.678) bpm for group C. There was a significant difference in heart rate between group L and group C, (consistent with the lower heart rate in group L patients), at all visits in the titration phase and up to visit V2 (24 to 48 hours) in maintenance phase 1. Thereafter, the

heart rate in patients in group C had also stabilised and there was no significant difference in heart rate between the groups after visit V3.
Values for mean blood pressure were comparable for both treatment groups, with no statistically significant differences for most of the visits, except the visit at 1 hour after treatment start. Values for systolic blood pressure were comparable for both treatment groups, with no statistically significant differences for most of the visits, except for visits at 1, 2, 4 and 6 hours after treatment start.
Values for diastolic blood pressure were comparable for both treatment groups, with no statistically significant differences for most of the visits, except at V3 (48-72 h, maintenance phase I) and V9 (day 9, maintenance phase II -24 h).

The time to heart rate response for the treatment groups was analysed by Kaplan – Meier analyses (log-rank test) and Cox proportional hazard model; for both, there is statistical difference between the treatment groups (p<.0001, hazard ratio 3.16 (95% CI: 1.96 to 5.11).

On the basis of HR at 24h (only in patients with HR measured at 24h), in group L 25/80 (31.3%) patients had a HR at 24h ≥ 95 bpm and 55/80 (68.8%) patients had a HR at 24h less than 95 bpm. In group C, 41/77 (53.2%) patients had a HR at 24h ≥ 95 bpm and 36/77 (46.8%) patients had a HR at 24h less than 95 bpm. The difference between the response rates was 22.3% (95% CI: 6.9% to 36.4%), demonstrating a statistically significant difference (p=0.0042) in the treatment groups on the basis of HR at 24 hours.

Subgroup analyses
An overview of subgroup analyses of the primary endpoint is shown in the figure below.

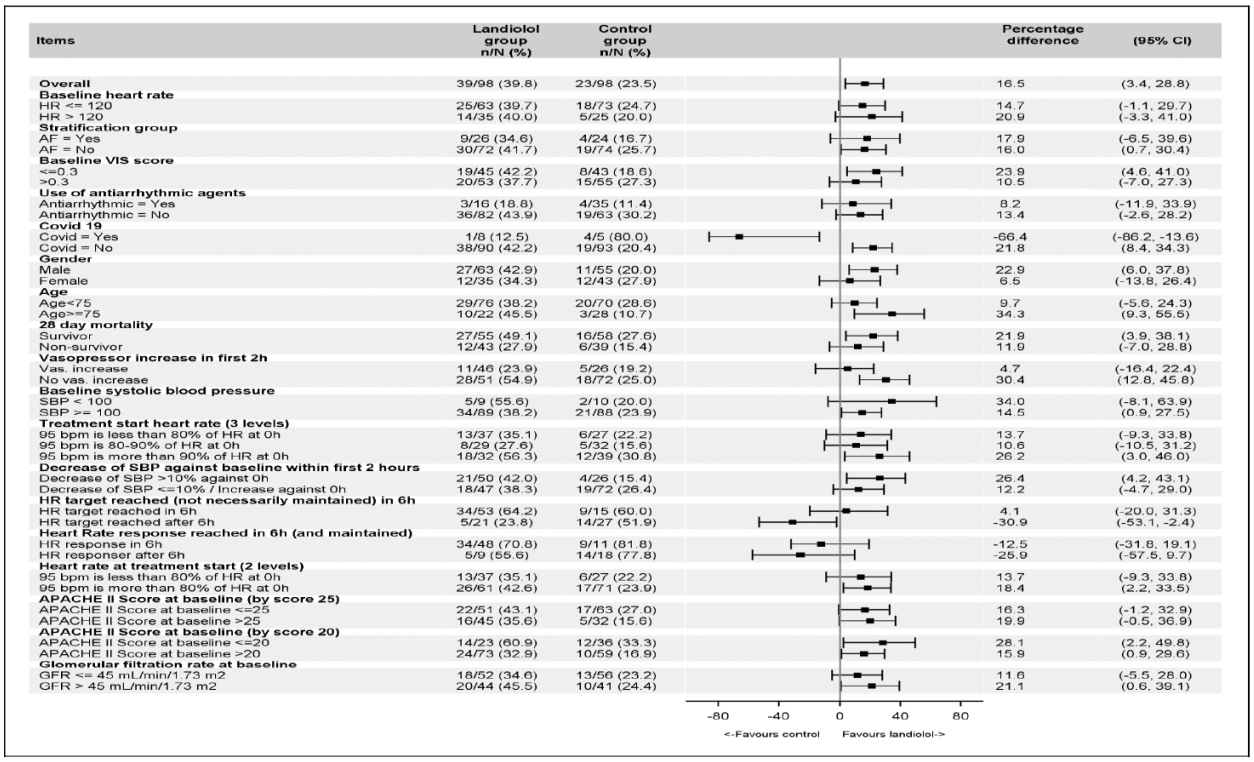

Figure 2: Forest plot for the primary response (FAS)

Subgroup analyses of 28-day mortality are shown in the figure below.

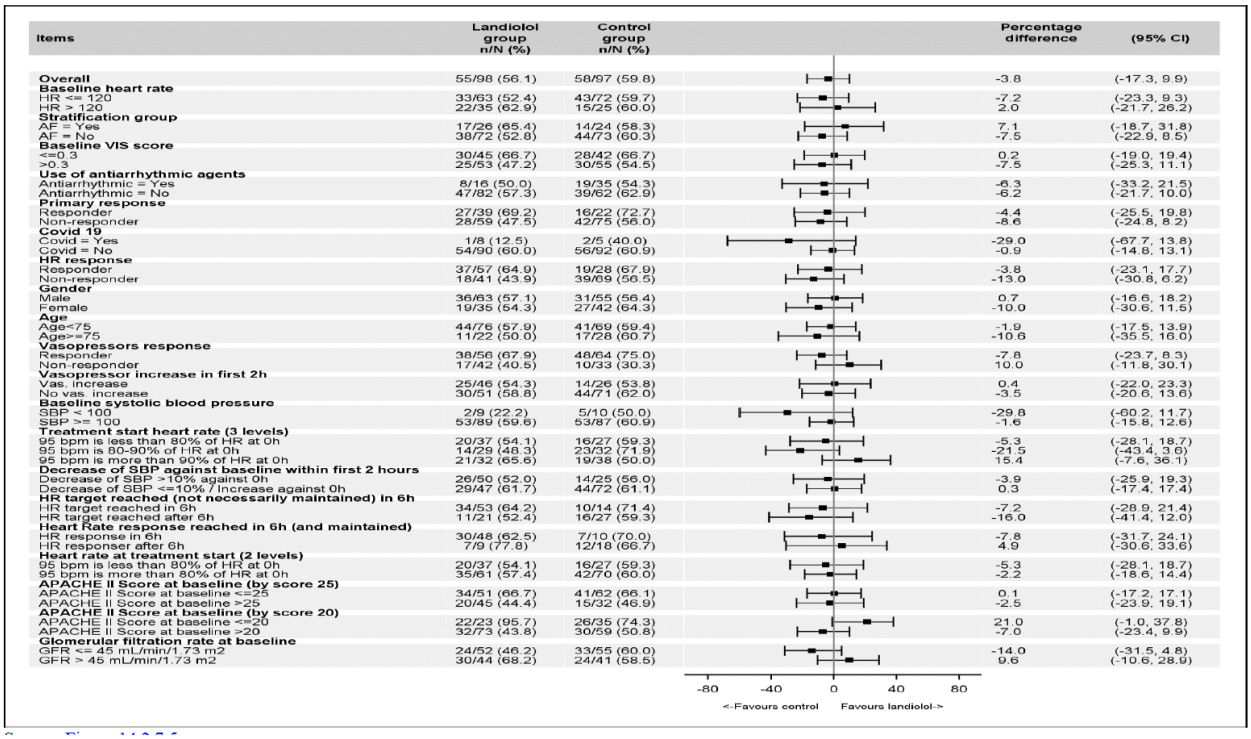

Figure 3: Forest plot for 28-day mortality (FAS)

Assessor's comment:

Sepsis is defined as organ dysfunction resulting from the dysregulation of the host's response to infection. Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (Rhodes, et al. 2017). Despite recent advances, the mortality rates for sepsis and septic shock remain as high as 30–50% (Vallabhajosyula, et al. 2018), with hospital mortality rates greater than 40% often reported for septic shock. Elevated HR has been associated with a poor outcome in septic shock, but it is unclear whether it is a surrogate of disease severity, or whether it plays a pathophysiological role that could be treated to improve patient outcomes. Recent clinical studies using esmolol in patients with sepsis suggest that control of HR can be safely achieved with beta-1-selective

beta-blockers. The use of intravenous beta-blocker in tachycardic septic patients has shown haemodynamic advantages (i.e. maintenance of heart rate within an acceptable range of 80–94 bpm, increase of stroke volume, maintenance of appropriate mean arterial pressure) compared to standard treatment (no treatment with beta-blockers). This was also associated with a reduction in norepinephrine requirements as well as an increase in cardiovascular performance and, eventually, an improvement in 28-day survival (Morelli, et al. 2013b).

The study population comprised adult patients in the ICU with septic shock, who remained tachycardic (HR ≥95 bpm) and required vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥65 mmHg after a haemodynamic optimisation period (at least 12 hours and up to 36 hours). Patients were randomised to one of two treatment groups. Patients in group C received standard treatment according to SSCG 2016 (this treatment was not specifically targeted to HR control). Patients in group L received standard treatment according to SSCG 2016 and treatment with LDLL300 for the duration of vasopressor

treatment. In the titration phase, which was the first 24 hours after treatment start, patients were administered LDLL300 at a starting dose of 1 µg/kg/min, with the dose progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min with a minimum dose interval of 20 minutes in order to obtain a target HR of 80-94 bpm.

A total of 200 patients with septic shock were enrolled in the study, at 20 sites in 7 countries in Europe. Of these, 196 randomised patients were treated in total, with 98 patients in each treatment group. The treatment groups were well balanced with no statistical differences determined between the treatment groups at screening (assessed by Wilcoxon, Fischer and t-test). The mean age was 64.4 (±12.5) years in group L and 65.2 (±15.06) years in group C, with a range of 23-93 years across the groups. The majority of patients enrolled in the study (99.5%) were white. A total of 26 (26.5%) patients in group L and 24 (245%) patients in group C had atrial fibrillation. The primary efficacy endpoint of the study was the heart rate response (HR = 80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start. The primary response was achieved in 39/98 (39.8%) patients in group L, compared to 23/98 (23.5%) patients in group C, with a difference between the response rates of 16.5% (95% CI: 3.4% to 28.8%), indicating that a statistically significantly (p=0.0133) higher proportion of patients in group L were responders achieving the primary response.

Despite a higher responder rate on the primary endpoint, there was no reduction in 28-day mortality found in the trial. The 28-day mortality rate was 43.9% for patients in group L and 40.2% for patients in group C. There was no significant difference (p=0.5954) in 28-day mortality rate between the treatment groups. The 28-day mortality rates are consistent with those reported in the literature for septic shock (Singer, et al. 2016; Vallabhajosyula, et al. 2018).

Similarly, ICU-mortality also did not differ (p=0.16) and the duration of hospital stay for patients alive on day 28 did not differ significantly (p=0.50) between treatment groups. The study data would suggest that despite achieving and maintaining the desired heart rate response effectively with LDLL300 treatment, the clinical decline may already too advanced in several patients to prevent mortality, or reducing heart rate does not provide the proposed benefit.

III.3.3. Clinical safety

A total of 166 treatment-emergent AEs (TEAEs) was reported after treatment in 66/98 [67.3%] patients in group L and 159 TEAEs were reported in 65/98 [66.3%] in group C in the study, with comparable incidence rates of 1.69 and 1.62 for Group L and Group C, respectively.

A total of 74 treatment-emergent SAEs were reported in 54/98 [55.1%] patients in group L and 68 were reported in 52/98 [53.1%] patients in group C. Two treatment-emergent SAEs in 2/98 [2.0%] patients in group L (one case each of low cardiac output syndrome and hypotension) were classified as being related to the study drug. Of the 166 TEAEs reported in group L, 14 AEs in 12/98 [12.2%] patients were classified as having a reasonable causal relationship with the study drug (i.e. related to treatment).

A total of 121 AEs in 55/98 (56.1%) patients in group L and 105 AEs in 48/98 (49.0%) patients in group C were classified as being related to the underlying disease (septic shock).
With regard to AE intensity, a total of 12/166 AEs reported in 9/98 [9.2%] patients in group L and 13/159 AEs, reported in 12/98 [12.2%] of patients in group C were mild in intensity. A total of 43/166 AEs reported in 23/98 [23.5%] patients in group L and 35/159 AEs, reported in 17/98 [17.3%] of patients in group C were moderate in intensity.
A total of 45/166 AEs reported in 22/98 [22.4%] patients in group L and 48/159 AEs, reported in 22/98 [22.4%] of patients in group C were severe in intensity.
A total of 21/166 AEs reported in 14/98 [14.3%] patients in group L and 23/159 AEs, reported in 18/98 [18.4%] of patients in group C were classified as life-threatening.
Two life-threatening AEs (low cardiac output syndrome and hypotension) each reported in 1/98 [1.0%] patient in group L were considered related to the study treatment.

A total of 45 fatal AEs occurred in 43/98 [43.9%] patients in group L (including 19 events of multiple organ dysfunction syndrome in 19/98 [19.4%] patients and 9 events of septic shock in 9/98 [9.2%] patients) and 40 fatal AEs occurred in 38/98 [38.8%] patients in group C (including 14 events of multiple organ dysfunction syndrome in 14/98 [14.3%] patients and 7 events of septic shock in 7/98 [7.1%] patients).
No fatal events were considered related to study treatment. An overview of TEAEs leading to fatality are shown below:

Table 9: All TEAEs leading to death by MedDRA preferred term within primary SOC

	Group L			Group C			AE related to study drug			AE not related to study drug		
							Group L			Group L		
MedDRA System Organ Class **Preferred term**	**AE**	**n (%)**	**IR**	**AE**	**n (%)**	**IR**	**AE**	**n (%)**	**IR**	**AE**	**n (%)**	**IR**
		N = 98			N = 98			N = 98			N = 98	
Any	45	43 (43.9%)	0.46	40	38 (38.8%)	0.41				44	42 (42.9%)	0.45
General disorders and administration site conditions	19	19 (19.4%)	0.19	14	14 (14.3%)	0.14				18	18 (18.4%)	0.18
Multiple organ dysfunction syndrome	19	19 (19.4%)	0.19	14	14 (14.3%)	0.14				18	18 (18.4%)	0.18
Infections and infestations	10	10 (10.2%)	0.10	13	13 (13.3%)	0.13				10	10 (10.2%)	0.10
Septic shock	9	9 (9.2%)	0.09	7	7 (7.1%)	0.07				9	9 (9.2%)	0.09
Pneumonia				3	3 (3.1%)	0.03						
Abdominal sepsis				1	1 (1.0%)	0.01						
COVID-19 pneumonia	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Necrotising fasciitis				1	1 (1.0%)	0.01						
Peritonitis				1	1 (1.0%)	0.01						
Cardiac disorders	5	5 (5.1%)	0.05	2	2 (2.0%)	0.02				5	5 (5.1%)	0.05
Cardiogenic shock	1	1 (1.0%)	0.01	2	2 (2.0%)	0.02				1	1 (1.0%)	0.01
Cardiac failure	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Cardiac failure acute	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Cardiopulmonary failure	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Myocardial infarction	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Vascular disorders	4	4 (4.1%)	0.04	1	1 (1.0%)	0.01				4	4 (4.1%)	0.04
Cerebral haemorrhage	2	2 (2.0%)	0.02							2	2 (2.0%)	0.02
Circulatory collapse	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Shock				1	1 (1.0%)	0.01						
Shock haemorrhagic	1	1 (1.0%)	0.01							1	1 (1.0%)	0.01
Hepatobiliary disorders	1	1 (1.0%)	0.01	3	3 (3.1%)	0.03				1	1 (1.0%)	0.01
Hepatic failure	1	1 (1.0%)	0.01	1	1 (1.0%)	0.01				1	1 (1.0%)	0.01
Acute hepatic failure				1	1 (1.0%)	0.01						
Perforation bile duct				1	1 (1.0%)	0.01						
Respiratory, thoracic and mediastinal disorders	1	1 (1.0%)	0.01	3	3 (3.1%)	0.03				1	1 (1.0%)	0.01

Respiratory failure				2	2 (2.0%)	0.02			
Acute respiratory distress syndrome				1	1 (1.0%)	0.01			
Respiratory disorder	1	1 (1.0%)	0.01				1	1 (1.0%)	0.01
Gastrointestinal disorders				3	2 (2.0%)	0.03			
Intestinal ischaemia				2	1 (1.0%)	0.02			
Pancreatic carcinoma				1	1 (1.0%)	0.01			
Injury, poisoning and procedural complications	2	2 (2.0%)	0.02				2	2 (2.0%)	0.02
Vasoplegia syndrome	2	2 (2.0%)	0.02				2	2 (2.0%)	0.02
Nervous system disorders	2	2 (2.0%)	0.02				2	2 (2.0%)	0.02
Brain injury	2	2 (2.0%)	0.02				2	2 (2.0%)	0.02
Metabolism and nutrition disorders	1	1 (1.0%)	0.01				1	1 (1.0%)	0.01
Hyperkalaemia	1	1 (1.0%)	0.01				1	1 (1.0%)	0.01
Surgical and medical procedures				1	1 (1.0%)	0.01			
Resuscitation				1	1 (1.0%)	0.01			

AE = count of adverse events, n (%) = count of patients (percentage out of all patients in analysis sets), IR = Incidence rate (number of AE per patient in the corresponding group)
Preferred term according to MedDRA version 24.0

A total of 21 AEs in 20/98 [20.4%] patients in group L led to study treatment discontinuation. Of these AEs, 8 events in 8/98 [8.2%] patients in group L were assessed by the Investigator as being related to the study treatment (4 cases of hypertension, 1 case each of bradycardia, low cardiac output syndrome, blood lactic acid increased and hepatic enzyme increased).

The most frequently reported AEs with a frequency > 5% patients in group L were multiple organ dysfunction syndrome [19.4%], septic shock [13.3%] and hypotension [11.2%].
In group C, the most frequently reported AEs (by PT) with a frequency > 5% were multiple organ dysfunction syndrome [14.3%], septic shock [9.2%], respiratory failure [7.1%] atrial fibrillation [6.1%], pneumonia [5.1%] and delirium [5.1%].

Clinical laboratory evaluation, haemodynamic evaluation and other safety assessments heamodynamic parameters, physical findings and other safety-related investigations revealed no additional safety concerns for Landiolol. There was a significant decrease in systolic blood pressure at 1 hour (p<.0001), 2 hours (p=0.0010), 4 hours (p=0.0487) and 6 hours (p=0.0342) after Landiolol administration in the titration phase in group L compared to group C. At all other visits there was no significant difference in systolic blood pressure between the groups. Values for systolic blood pressure were comparable for both treatment groups
There were 16 AEs of new onset arrythmia in 13/98 [13.3%] patients in group L with an incidence ratio of 0.16, compared to 22 AEs in 17/98 [17.3%] patients in group C with an incidence ratio of 0.22, with no significant difference between the groups (p=0.5523).

Safety results were comparable for patients in both treatment groups with respect to AE rates, seriousness, intensity and outcome.

Treatment-emergent adverse events from the SOC Cardiac disorders observed in the LANDI-SEP Study are in line with the known safety profile of Landiolol (SmPC Rapibloc®). With regard to the AEs judged related to study treatment, Bradycardia has been reported as a common expected AE after Landiolol treatment (≥ 1/100 to < 1/10). The event of low cardiac output syndrome is a known rare event (≥ 1/10,000 to < 1/1,000).
Specific treatment of patients with cardiac dysfunction (for example after cardiac surgery, during ischemia or in septic states) is addressed under “special populations” in the SmPC, with recommended dosing outlined. Treatment-emergent adverse events from the SOC Vascular disorders observed in the LANDI-SEP Study are also in line with the known safety profile of Landiolol (SmPC Rapibloc®). Hypotension is a common expected AE after Landiolol treatment (≥ 1/100 to < 1/10).

The safety profile of Landiolol is consistent with clinical data in the SmPC. The exceptions are blood lactate increased, polyuria and cardiac dysfunction, which were observed in this study and are not included in the SmPC. No additional safety concern was detected for Landiolol on the basis of haemodynamic parameters, physical findings and other safety-related investigations during the study.

Assessor's comment:
Most AEs in patients in group L (121 AEs in 56.1% patients) and group C (105 AEs in 49.0% patients) were judged related to the underlying disease, septic shock. The most frequently reported AEs with a frequency > 5% in group L were multiple organ dysfunction syndrome [19.4%], septic shock [13.3%] and hypotension [11.2%]. In group C, the most frequently reported AEs (by PT) with a frequency > 5% were multiple organ dysfunction syndrome [14.3%], septic shock [9.2%], respiratory failure [7.1%] atrial fibrillation [6.1%], pneumonia [5.1%] and delirium [5.1%]. A total of 43 (43.9%) patients in group L and 39 (40.2%) patients in group C died during the study, with no significant difference in mortality rates between the groups. The cause of death was attributed to the underlying disease and its consequences (septic shock and multiple organ dysfunction syndrome), with no fatal events considered related to study treatment.

III.3.4. Risk management plan (RMP)

The MAH has submitted an updated risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to landiolol Orpha Devel.

The MAH has submitted two RMP versions during this procedure:
- vOD1.1 is a minor version (for preliminary HA's review), with data lock point 02.02.2023, signed on 29.04.2024, submitted to HA on 15.05.2024, approved on 27.06.2024 (the date when MAH received the confirmation regarding the timetable for the next step of this procedure);
- vOD2.0 is a major version, with the same data lock point 02.02.2023, signed on 29.10.2024, submitted to HA on 31.10.2024, approved on 07.11.2024.

These two versions are identical in changes.
Summary of significant changes are: harmonisation with V3.0 EU RMP for DCP1 (MAH Amomed Pharma GmbH) upon PVAR in course of Rapibloc type II variation (II026G) and update of safety concerns:
Removal of:
- Important identified risk "severe hypotension"
- Important identified risk "severe bradycardia"
- Important identified risk "cardiac arrest"
- Missing information "Use in paediatric population (<18 years old)"

Final data from the completed LANDI-SEP clinical trial was added.
Update of epidemiology data and references

Landiol Orpha Level is authorised since 20 December 2023 through a full application, Art 8(3), procedure. Part II of the RMP is in line with GVP V rev. 2, all modules are provided. This RMP is similar to the currently approved RMP of Rapibloc version 3.0, dated 28 February 2024 (for MAH: Amomed Pharma GmbH).

Safety specification

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and breastfeeding

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the MAH, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the MAH, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version vOD2.0 signed 29.10.2024 is considered acceptable.

III.3.5. Product information

Summary of Product Characteristics

The changes proposed are considered acceptable.

Package leaflet and user test

The changes proposed are considered acceptable. However, all comments on de SmPC should be implemented, if necessary, in the package leaflet.

Labelling

N/A

IV. OVERALL CONCLUSION AND BENEFIT RISK DISCUSSION

Sepsis is defined as organ dysfunction resulting from the dysregulation of the host's response to infection. Septic shock is defined as a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality (Rhodes, et al. 2017). Despite recent advances, the mortality rates for sepsis and septic shock remain as high as 30–50% (Vallabhajosyula, et al. 2018).

Landiolol is an ultra-short acting beta-1-selective adrenergic antagonist. Since Landiolol is a highly beta-1-selective, ultrashort-acting beta-blocker, it could be ideally suited for the treatment of critically ill patients, due to its limited hypotensive effect. The aim of this LANDI-

SEP study was to demonstrate, in a multicentre setting, that administration of Landiolol in patients with septic shock and persistent tachycardia/ tachyarrhythmia is effective in reducing and maintaining heart rate without increase in vasopressor requirements. The current indication of landiolol is as follows:

"Landiolol is indicated in adults 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.*
- *Non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention.*

Landiolol is not intended for use in chronic settings."

In this type II variation, no extension of the indication is requested. The MAH does proposes to update the posology for patients with sepsis, based on the results of the LANDI-SEP trial.

The primary efficacy endpoint of the study was the heart rate response (HR = 80-94 bpm) and maintenance thereof and no increase in vasopressor requirements during the first 24 hours after treatment start. The primary response was achieved in 39/98 (39.8%) patients in group L, compared to 23/98 (23.5%) patients in group C, with a difference between the response rates of 16.5% (95% CI: 3.4% to 28.8%), indicating that a statistically significantly (p=0.0133) higher proportion of patients in group L were Responders achieving the primary response. Despite a higher responder rate on the primary endpoint, there was no reduction in 28-day mortality found in the trial. The 28-day mortality rate was 43.9% for patients in group L and 40.2% for patients in group C. There was no significant difference (p=0.5954) in 28-day mortality rate between the treatment groups. The 28-day mortality rates are consistent with those reported in the literature for septic shock (Singer, et al. 2016; Vallabhajosyula, et al. 2018).

In LANDI-SEP Landiolol was confirmed to be effective in reducing and maintaining heart rate in patients with septic shock and persistent tachycardia/tachyarrhythmia, with no increase in vasopressor requirements during the first 24 hours after treatment start in the majority of patients. Unfortunately no benefit on mortality or ICU stay duration was shown however. The safety profile of Landiolol is consistent with clinical data in the SmPC. No additional safety concern was detected for Landiolol on the basis of haemodynamic parameters, physical findings and other safety-related investigations during the study.

The provided data from the LANDI-SEP trial provided additional data on use of landiolol in patients with sepsis and can be used to further guide the posology. The proposed addition to the posology section is largely in alignment with the posology used in the LANDI-SEP trial, where patients were the starting dose was 1 µg/kg/min and the dose was progressively increased at increments of 1 µg/kg/min to a maximum of 40 µg/kg/min. However, in the clinical trial treatment with landiolol was only given during vasopressor treatment and stopped after discontinuation, which is not reflected in the proposed posology. Therefore, the MAH has been requested to either justify the omission of "during vasopressor treatment", or include the text in the proposed posology of the SmPC. The MAH has chosen the latter option and has revised the concerned section by changing *"patients with septic shock"* to *"patients*

with septic shock receiving vasopressor therapy". The outstanding OC has therewith been resolved.

No extension of the indication is requested and the overall benefit-risk balance for landiolol remains positive. See the separate SmPC document for more details on the proposed changes.

V. OVERALL CONCLUSION

The type II variation is approvable if the MAH provides a revised Patient Information Leaflet. As requested, the MAH submitted the revised Summary of Product Characteristics, Labelling or Package Leaflet including the approved changes of this variation.