CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217202Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	217202
Submission type	New drug application resubmission
Submission date	May 29, 2024
Brand name	To be determined
Generic name	Landiolol
Sponsor	AOP Orphan Pharmaceuticals GmbH
Primary reviewer	Li Wang, PhD
Secondary reviewer	Doanh Tran, PhD

BACKGROUND

The Applicant, AOP Orphan Pharmaceuticals GmbH, is developing landiolol which is indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. The new drug application (NDA) was originally submitted on May 31, 2022. The complete response letter was issued on May 23, 2023 due to the deficiencies identified for drug product and manufacturing. Refer to the complete response letter dated May 23, 2023 for NDA 217202 in DARRTS for more details.

In the original submission, the Applicant did not investigate the inhibitory effect of landiolol and its metabolite M1 on the activity of multiple drug transporters. Inhibition of these drug transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE) proteins (MATE1, MATE2-K), organic anion transporter (OAT)1, and OAT3, by landiolol and/or its metabolite M1 may have an impact on the systemic exposure of concomitantly administered drugs that are sensitive substrates of these transporters. Consequently, a postmarketing requirement (PMR) had been proposed by the clinical pharmacology review team described in the complete response letter:

Conduct an in vitro assessment to evaluate the potential of landiolol and its M1 metabolite to inhibit drug transporters including P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, OAT1, and OAT3.

The Applicant resubmitted the NDA on May 29, 2024. In the package, the Applicant confirms that the inhibitory effect of landiolol and its metabolite M1 on P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, OAT1, and OAT3 will be investigated if NDA 217202 is approved. The Applicant also (b) (4)

RECOMMENDATION

The Office of Clinical Pharmacology has (b) (4) .

REVIEW

(b) (4)

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(b) (4)

REVIEWER'S COMMENTS:

1. Landiolol mean peak plasma concentration (C_{max}) with intravenous (iv) infusion at the highest proposed infusion rate (37.3 mcg/kg/min) is 1.96 µM. (b) (4)

2. M1 mean C_{max} with iv infusion at the infusion rate of 9.3 mcg/kg/min is 1.84 µM (the molecular weight of M1 is 395 g/mol). As landiolol pharmacokinetics increases dose-proportionally at the dosage range of 9.3 to 74.6 mcg/kg/min, M1 C_{max} with iv infusion at the highest proposed infusion rate (37.3 mcg/kg/min) is projected to be 7.39 µM. (b) (4)

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/s/

LI WANG
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Clinical Pharmacology Review

NDA Number	217202
Link to EDR	\\CDSESUB1\evsprod\NDA217202
Submission Date	May 31, 2022
Submission Type	Standard
Brand Name	
Generic Name	Landiolol
Dosage Form and Strength	White to almost white lyophilized powder in a single-dose vial containing 280 mg of landiolol (equivalent to 300 mg landiolol HCl).
Route of Administration	Intravenous administration
Proposed Indication	Landiolol is indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.
Applicant	AOP Orphan Pharmaceuticals GmbH
Associated IND	Not applicable
OCP Review Team	Li Wang, Ph.D. and Snehal Samant, Ph.D.
OCP Final Signatory	Shirley K. Seo, Ph.D. Division Director Division of Cardiometabolic and Endocrine Pharmacology

Contents

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1. EXECUTIVE SUMMARY

The Applicant (AOP Orphan Pharmaceuticals GmbH) submitted NDA 217202 on May 31, 2022 via the 505(b)(2) pathway, seeking approval of landiolol, a beta adrenergic blocker, for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. The drug product is 280 mg of landiolol (equivalent to 300 mg of landiolol HCl) as a lyophilized powder in a single-dose vial to be reconstituted with 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for intravenous (iv) administration. Landiolol was originally developed by Ono Pharmaceutical Co. in Japan with the trade name Onoact® 50 for injection and was approved for marketing in Japan in 2002. Landiolol was approved (developed by AOP independently from Ono) for marketing in Europe in 2016 (with AOP as the sponsor). This NDA is recognized as an original (NME) NDA submission as Landiolol has not been approved in US.

In this submission, the Applicant is primarily relying on eight scientific publications to support efficacy and safety of landiolol. Additionally, the Applicant submitted the results of *in vitro* assessments to evaluate cytochrome P450 (CYP)-mediated drug-drug interaction (DDI) potential of landiolol, three pharmacokinetics (PK)/ pharmacodynamics (PD) studies in healthy Caucasian subjects and one PK/PD study in patients with tachycardic atrial fibrillation or atrial flutter. The Applicant also relies on scientific publications to support the proposed dosing and other clinical pharmacology information. Key issues addressed in this clinical pharmacology review are:

1) Appropriateness of the proposed dose of landiolol.
2) Appropriateness of the proposed dosing recommendations in patients with renal and hepatic impairment.
3) Assessment of drug interaction potential of landiolol.
4) Assessment of the adequacy of the PK bridge between the clinical trial formulations and the to-be-marketed formulation of landiolol.

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1.1 Recommendations

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in NDA 217202. This NDA is considered approvable from a clinical pharmacology perspective.

Clinical pharmacology pertinent key review issues with specific recommendations and comments are summarized below:

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>General dosing instructions</td><td>Administer landiolol as a continuous intravenous infusion, titrating as needed for heart rate control. There is limited information on clinical efficacy and safety of landiolol with iv infusion of landiolol beyond 24 hours.

Recommended Dosing
<table><tr><th></th><th>Normal cardiac function</th><th>Impaired cardiac function (b) (4)</th></tr><tr><td>Starting dose</td><td>9.3 mcg/kg/min</td><td>(b) (4) mcg/kg/min</td></tr><tr><td>Titration interval</td><td>10 min</td><td>15 min</td></tr><tr><td>Titration step</td><td>9.3 mcg/kg/min</td><td>(b) (4) mcg/kg/min</td></tr><tr><td>Maximum dose</td><td>37.3 mcg/kg/min</td><td>37.3 mcg/kg/min</td></tr></table>9.3 mcg/kg/min landiolol is equivalent to 10 mcg/kg/min landiolol hydrochloride</td></tr>
</table>

Dosing in patient subgroups (intrinsic and extrinsic factors)	**Hepatic Impairment:** Labeling recommendation: The effect of landiolol on clinical outcomes in patients with hepatic impairment (Child-Pugh B or C) has not been studied. Avoid use of landiolol in patients with hepatic impairment (Child-Pugh B or C). The Applicant provided information on the impact of hepatic impairment on pharmacokinetics of landiolol from a scientific publication. As most of the subjects with hepatic impairment (5 out of 6) in the study were recognized as having mild hepatic impairment (Child-Pugh class A), the effect of moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) on the PK of landiolol is not clear. A clinical study has not been conducted to date to characterize this effect. As landiolol is proposed to be used as single dose in patients with an urgent clinical situation and the terminal half-life is very short, no PMR is required. **Drug interaction:** There is a lack of information on the DDI potential due to transporter inhibition by landiolol and its metabolite M1. A PMR will be issued to request the Applicant to conduct an in vitro assessment to evaluate the potential of landiolol and its M1 metabolite to inhibit the following drug transporters: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE) proteins (MATE1, MATE2-K), organic anion transporter (OAT)1, and OAT3.
Labeling	The proposed labeling language pertaining to clinical pharmacology is generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The Applicant did not conduct a relative bioavailability study comparing the to-be-marketed and clinical trial formulations. Given the high water solubility of landiolol, relatively simple formulations, similar excipients and active to inactive ingredient ratio, significant differences in the bioavailability between the two formulations are not expected for the parenteral solution

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	intended solely for administration by intravenous injection.

1.2 Post-marketing Requirements and Commitments

1. Conduct an *in vitro* assessment to evaluate the potential of landiolol and its metabolite M1 to inhibit the following drug transporters: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE) proteins (MATE1, MATE2-K), organic anion transporter (OAT)1, and OAT3.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Clinical Pharmacology Findings

In the submission of NDA 217202, the Applicant has conducted four clinical PK/PD studies (three in healthy subjects and one in patients), and three *in vitro* studies. Additionally, the Applicant has referenced eight scientific publications. The clinical pharmacology review focuses on reviewing the dose-response data from two publications (Yoshiya *et al.*, 2000 and Kato *et al.*, 1997), *in vitro* DDI assessment from Studies 100058422, 100059009, and 100059780 and, pharmacokinetics of landiolol in subjects with hepatic impairment from a publication by Takahata *et al.*, 2005. Summarized below are the key clinical pharmacology findings from the submitted studies and references:

Absorption

- Landiolol exposure, including C_{max} and AUC increases in a dose-proportional manner with doses ranging from 9.3 to 74.6 mcg/kg/min.

Distribution

- Landiolol is distributed into tissues to some extent following iv administration, with steady-state volume of distribution of 0.28-0.37 L/kg.
- Landiolol exhibits low protein binding to human plasma protein (<10%) [reference appendix 4.3: Tsunekawa *et al.*,].

Elimination

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- The mean terminal half-life ($t_{1/2}$) of approximately 3-4.5 minutes.
- Landiolol is mainly metabolized in the plasma by pseudocholinesterases and in the liver/intestine/kidney by carboxylesterases. Hydrolysis of the ester moiety releases a ketal (the alcoholic component) that is further cleaved to yield glycerol and acetone, and the carboxylic acid component (metabolite M1), which subsequently undergoes beta-oxidation to form metabolite M2 (a substituted benzoic acid) [reference appendix 4.3: Tsunekawa *et al.*,].

***Intrinsic Factors*:**

- Compared to subjects with normal hepatic function, the geometric mean AUC and C_{max} of landiolol were increased by 44% and 42%, respectively, in subjects with impaired hepatic function (primarily Child-Pugh A).

***Drug Interactions*:**

- *In vitro* assessment demonstrated that landiolol and the metabolite M1 are time-dependent inhibitors of CYP2D6.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The Applicant originally proposed the dosing regimen as follows

Dosing for patients with normal cardiac function:

- (b) (4)

Dosing for patients with impaired cardiac function (b) (4):

- (b) (4)

- [redacted] (b) (4)

During the mid-cycle communication, the clinical review team requested the applicant to provide the data in support of [redacted] (b) (4) [redacted] (Reference: Mid-cycle communication DARRTS 12/14/2022)

The recommended dosage and administration are as follows (Table 1):

Administer landiolol as a continuous intravenous infusion, titrating as needed for heart rate control. There is little experience beyond 24 hours.

Table 1. Dosing Scheme.

	Normal cardiac function	**Impaired cardiac function** [redacted] (b) (4)
Starting dose	9.3 mcg/kg/min	[redacted] (b) (4) mcg/kg/min
Titration interval	10 min	15 min
Titration step	9.3 mcg/kg/min	[redacted] (b) (4) mcg/kg/min
Maximum dose	37.3 mcg/kg/min	37.3 mcg/kg/min

9.3 mcg/kg/min landiolol is equivalent to 10 mcg/kg/min landiolol hydrochloride

2.2.2 Therapeutic individualization

- No dose adjustment is needed in patients based on age, body weight, gender, or race/ethnicity.
- No dose adjustment is necessary in patients with mild hepatic impairment. The effect of landiolol on clinical outcomes in patients with hepatic impairment (Child-Pugh B or C) has not been studied. Avoid use of landiolol in patients with hepatic impairment (Child-Pugh B or C).
- No dose adjustment is needed for patients on landiolol who are receiving concomitant drugs which are CYP substrates.

See Sections 3.3.3 and 3.3.4 for more details.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The following edits are recommended for Sections 8 and 12:

- [redacted] (b) (4)
- Section 12.2 Pharmacodynamic: Revise the content [redacted] (b) (4). Check the requirements at FDA Guidance on Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format when you revise this section.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Landiolol, a new molecular entity, is developed as lyophilized powder with 280 mg of landiolol in a single-dose vial for iv injection. Landiolol is a short-acting β1-selective adrenoceptor antagonist indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter. Landiolol hydrochloride was originally developed by the Japan-based Ono Pharmaceutical Co. for the Japanese prescription drug market with the trade name Onoact® 50 for injection. It was then approved for marketing (developed by AOP independently from Ono) through the decentralized process in Europe in 2016. The Applicant filed this NDA via the 505(b)(2) regulatory pathway on May 31, 2022. The evidence in support of landiolol's effectiveness is derived primarily from eight scientific publications.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Landiolol is a short-acting β1-selective adrenoceptor antagonist.
Mechanism of action	Landiolol is a selective beta-1-adrenoreceptor antagonist that inhibits the positive chronotropic effects of the catecholamines adrenaline and noradrenaline on the heart, where beta-1-receptors are predominantly located.
Active moieties	Landiolol
	General Information

Characteristic	Drug Information
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentrations of landiolol in human plasma.
Healthy subjects versus patients	Not applicable.
Drug exposure at steady state following the therapeutic dosing regimen	In patients with atrial fibrillation or atrial flutter, peak plasma concentrations ranged from 0.52 to 1.77 mcg/mL and 0.51 to 3.33 mcg/mL following the iv infusion dose of 37.3 and 74.6 mcg/kg/min, respectively.
Dosage proportionality	Landiolol pharmacokinetics increases in a dose-proportional manner over a range of 9.3 and 37.3 mcg/kg/min
Time to achieve steady state	Steady-state PK was achieved ~15 min [reference appendix 4.3: Nakashima *et al.*,].
Bridge between to-be-marketed and clinical trial formulations	No bioequivalence study was conducted to compare Onoact ® 50 mg and Landiolol HCl 300 mg formulations. Given the high water solubility of Landiolol, relatively simple formulations, similar excipients and active to inactive ingredient ratio, significant differences in the bioavailability and are not expected for the parenteral solution intended solely for administration by intravenous injection.
	Distribution
Volume of distribution	The volume of distribution of landiolol is 0.3-0.4 L/kg and 0.4 L/kg.
Plasma protein binding	Protein binding of landiolol in human plasma is <10%.
Drug as substrate of transporter	Not tested.
	Elimination
Mass balance results	In humans, the main excretion pathway of landiolol is urine. By 24 hours after a 60 min continuous infusion period, 89 to 99% of landiolol and its major metabolites M1 and M2 are excreted in urine. At 4 hours after a 60 min landiolol intravenous infusion period approximately 50 to 75% of the administered dose (approximately half of this as metabolite M1, 8 to 12% as metabolite M2, and 8% as parent) is recovered in urine.
Clearance	The total body clearance of landiolol was (b) (4) 57 mL/kg/min at steady state after a 20-hour continuous landiolol infusion of 37.3 mcg/kg/min.
Half-life	The elimination $t_{1/2}$ of landiolol was (b) (4) 4.5 minutes after a 20-hour continuous landiolol infusion of 37.33 mcg/kg/min.
Metabolic pathway(s)	Landiolol is mainly metabolized in the plasma by pseudocholinesterases and in the liver/intestine/kidney by carboxylesterases.
	Intrinsic Factors and Specific Populations
Hepatic impairment	Compared to subjects with normal hepatic function, the geometric mean AUC and C_{max} of landiolol were increased by 44% and 42%, respectively, in subjects with impaired hepatic function (primarily Child-Pugh A).
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	*In vitro* assessment demonstrated that landiolol and the metabolite M1 are time-dependent inhibitors of CYP2D6.
Inhibition/induction of transporter systems	Not tested

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology program provide supportive evidence of effectiveness?

The evidence in support of landiolol's effectiveness to reduce heart rate (HR) is derived primarily from eight scientific publications which are all comprised of clinical trials that contain some dose-ranging data (Table 2). Overall, participants in the landiolol group had a greater proportion of patients with at least moderate improvement (paroxysm ceased intermittently or heart rate reduction ≥20%) than those in placebo group. Please refer to clinical review by Dr. Mitchell Psotka for more information.

Table 2. Summary of Publications Used to Support Efficacy for Landiolol.

Publications	Sample size	Population	Dose	Efficacy
Kato *et al.*, 1997	L: 50 P: 49	Hospitalized paroxysmal atrial fibrillation (non-surgical) & onset within 2 weeks & HR>100 bpm for ≥5 min & BP >100/70 mmHg	➢ i.v. bolus: 250 µg/kg ➢ i.v. infusion: 80 µg/kg/min for 10 min	L: 60% P: 2% @11 minutes
Yoshiya *et al.*, 1997	L: 136 P: 144	Ischemic heart disease or hypertension, undergoing surgery, with HR≥100 ≥1 min (SVT) or ≥3 min (Sinus) during anesthesia	➢ i.v. bolus: 125 µg/kg ➢ i.v. infusion: 40 µg/kg/min for 10 min	L: 80% P: 9% @5 minutes
Yoshiya *et al.*, 2002	L: 29 P: 29	Ischemic heart disease or hypertension undergoing surgery with perioperative tachyarrythmia HR≥120 ≥3 min or HR≥100 & RPP≥15000 for ≥3 min or ST changes	➢ i.v. bolus: 125 µg/kg ➢ i.v. infusion: 40 µg/kg/min for 10 min	L: 86% P: 10% @11 minutes
Tanaka *et al.*, 2008	L: 8 P: 4	Patients with ischemia and HR HR≥120 for ≥1min, with ST changes on ECG (3 min if sinus tachycardia)	➢ i.v. Bolus: 30, 60, and 125 µg/kg ➢ i.v. infusion: 10, 20, and 40 µg/kg/min for 10 min	L: i.v. bolus (30-60 µg/kg) followed by i.v. infusion (10-20 µg/kg/min): 80% i.v. bolus (60-125 µg/kg) followed by i.v. infusion (20-40 µg/kg/min): 67% P: 0 @11-22 minutes
Taenaka & Kikawa 2013	L: 106 P: 54	Ischemic heart disease or hypertension, undergoing surgery, with HR≥100 ≥1 min (postoperative supraventricular	➢ i.v. bolus: 30, 60, and 125 µg/kg ➢ i.v. infusion: 10, 20, and 40 µg/kg/min for 10 min	L: i.v. bolus (30-60 µg/kg) followed by i.v. infusion (10-20 µg/kg/min): 60%

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		tachyarrhythmias) or ≥3 min (Sinus) during anesthesia		i.v. bolus (60-125 µg/kg) followed by i.v. infusion (20-40 µg/kg/min): 42% P: 0 @11-22 minutes
Sakamoto *et al.*, 2012	L: 35 D: 36	Post-operative atrial fibrillation or flutter HR≥100 for ≥5 min after open-heart surgery	➢ L: i.v. infusion at 0.5-40 µg/kg/min for 24 hours ➢ D: An i.v. bolus dose of 0.25 mg/kg over 2 min, followed by an initial rate of 3 mg/h that was titrated to a maximum rate of 15 mg/h	L: 97% D: 78% @24 hrs
Nagai *et al.*, 2013	L: 93 Dig: 107	NYHA III-IV & atrial fibrillation or flutter, HR≥120, LVEF 25-50%, SBP≥90 mmHg	➢ L: i.v. infusion at 1-10 µg/kg/min for 2-72 hours ➢ Dig: 0.25 mg IV (starting dose), could be uptitrated within 72 h according to the patient's condition	L: 48% Dig: 14% @2 hrs
Kakihana *et al.*, 2020	L: 75 C: 75	ICU Sepsis & atrial fibrillation, flutter, or sinus tachycardia HR≥100 for ≥10 min	➢ L: i.v. infusion at 1-20 µg/kg/min for 96 hours	L: 86% P: 10% @96 hrs

Notes: L: Landiolol; P: Placebo; C: Control with standard of care; D: Diltiazem; Dig: Digoxin.

Efficacy: ≥20% reduction in heart rate from baseline or heart rate decreased to ≤100 bpm, or paroxysm terminated intermittently

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed titration dosing regimen for patients with normal cardiac function includes a starting iv infusion dose of 9.3 mcg/kg/min for 10 min. If necessary, increase the dose up to 37.3 mcg/kg/min in 10 mcg/kg/min increments no sooner than 10 min after the last dose increase on an individual patient basis. The Applicant provided supporting dose-response information for landiolol from two publications (Yoshiya *et al.*, 2000 and Kato *et al.*, 1997). In the paper reported by Yoshiya *et al.*, in 2000, the primary efficacy (paroxysm ceased intermittently or heart rate reduction ≥20%) endpoint was evaluated in surgical patients with tachycardia with heart rates ≥100 bpm during anesthesia among three dose groups, namely 10-minute infusion of 9.3, 18.6, and 37.3 mcg/kg/min doses, each following a loading bolus dose (See Appendix 4.2 for details). After starting the iv infusion of landiolol, a rapid drop in the heart rate was observed

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and the heart rate at 11 min of iv infusion was significantly lower than that at pre-administration status in all the dose groups. When comparing the mean heart rate among the three dose groups, a significant difference was observed between the two dose levels 9.3 mcg/kg/min vs. 37.3 mcg/kg/min. The proportion of patients achieving the efficacy endpoint were 67%, 78%, and 91% at doses of 9.3, 18.6, and 37.3 mcg/kg/min, respectively. The difference in proportion of patients achieving the efficacy endpoint was statistically significant among the three groups based on Cochran-Armitage trend test.

In the publication by Kato *et al.*, in 1997, the primary efficacy (paroxysm ceased intermittently or heart rate reduction ≥20%) was tested in subjects with paroxysmal atrial fibrillation/flutter (PAF/PAFL) or paroxysmal supraventricular tachycardia (PSVT) among three dose groups, namely 10-minute infusion of 18.6, 37.3, and 74.6 mcg/kg/min doses, each following a loading bolus dose (See Appendix 4.2 for details). For subjects with PAF/PAFL, there was a rapid reduction in heart rate when iv infusion of landiolol started and the heart rate at 6 and 11 min of iv infusion was significantly lower than that at pre-administration status in all three dose groups. The proportions of patients achieving the primary efficacy endpoint were increased with increasing dose, shown as 55.6%, 61.9%, and 69.2% at the dose of 18.6, 37.3, and 74.6 mcg/kg/min, respectively. However, the difference in proportion of patients achieving the efficacy endpoint was not statistically significant among the three groups based on Cochran-Armitage trend test. For subjects with PSVT, however, a clear dose-response relationship was not observed. The proportion of patients achieving the efficacy endpoint were 47.1%, 57.1%, and 47.4% at doses of 18.6, 37.3, and 74.6 mcg/kg/min, respectively. The reason why there is a lack of dose-response relationship for PSVT patients is not known. Overall, the study designs and sample size of the two published studies are considered acceptable. Dose-response information for patients with impaired cardiac function (b) (4) was not available. The Applicant proposed a titration dosing regimen for patients with impaired cardiac function (b) (4) as supported by the scientific publication by Kakihana *et al.*, (2020), whereas the proposed maximum infusion dose was (b) (4) mcg/kg/min.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Effect of Renal Impairment

The effect of renal impairment on the PK of landiolol has not been tested. However, adjustment of the dose of landiolol in patients with renal impairment is not warranted as landiolol is used for

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single iv infusion up to 24 hours and renal excretion is not the major elimination pathway for landiolol (<10%).

Effect of Hepatic Impairment

The Applicant referenced a scientific publication by Takahata *et al.* (2005) to provide information on the effect of hepatic impairment on the PK of landiolol. There were 12 subjects enrolled in the study, with 5 subjects characterized as having mild hepatic impairment (Child-Pugh class A), 1 subject was characterized as having moderate hepatic impairment (Child-Pugh class B), and 6 subjects with normal hepatic function. All subjects received a 1-minute loading infusion of 0.06 mg/kg/min, followed by a 60-minute infusion of 0.02 mg/kg/min. Compared to subjects with normal hepatic function, the geometric mean AUC and C_{max} of landiolol were increased by 44% and 42%, respectively, in subjects with impaired hepatic function. Adjustment of the starting dose of landiolol in patients with mild hepatic impairment is not needed as the clinical dose level of landiolol is up to 74.6 mcg/kg/min and the exposure expected at that dose would be well above the magnitude of increase expected with patients who have mild hepatic impairment at the standard starting dose of 9.3 mcg/kg/min [reference appendix 4.2: Kato *et al.*,]. Because most of the subjects with hepatic impairment (5 out of 6) in the study were recognized as Child-Pugh Class A, the effect of moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) on the PK of landiolol is not clear. A clinical study has not been conducted to date to characterize this effect. As landiolol is proposed to be used as single dose in patients with an urgent clinical situation and the terminal half-life is very short, no PMR is required.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

In vitro studies for drug metabolizing enzyme based DDI

- Landiolol is primarily metabolized by pseudocholinesterases and carboxylesterases. Therefore, the risk of drug interaction between landiolol with inhibitors and/or inducers of CYP enzymes is low.
- Landiolol is an *in vitro* reversible inhibitor of CYP2C19 (IC_{50} = 69 µM), CYP2D6 (IC_{50} > 100 µM), and CYP3A4 (IC_{50} > 100 µM). The clinically relevant concentration (unbound $C_{max,ss}$) was 3.12 µM based on the highest dose of 40 mcg/kg/min used in Study LDLL600.201) and the drug interaction index R_1 was calculated as 1.05. Given that the calculate R_1 is close to cut-off value (1.02) and landiolol with short elimination $t_{1/2}$ (3.0-4.5 min) is used for single iv infusion up to 24 hours, landiolol is not likely to exert inhibitory effect on CYP2C19 activity in vivo.

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- Landiolol is an *in vitro* time-dependent inhibitor of CYP1A and CYP2D6, with 21.0% and 54.9% inhibition at 100 μM. Given that landiolol showed 54.9% inhibition at super-therapeutically relevant concentrations (100 μM) and landiolol is used for single iv infusion up to 24 hours, landiolol is not likely to exert time-dependent inhibitory effect on CYP2D6 activity *in vivo*.
- The major circulating metabolites, M1 was not reversible inhibitor of the major CYPs evaluated and demonstrated similar time-dependent inhibition potential for CYP1A and CYP2D6.

In vitro studies for drug transporter based DDI.

The Applicant did not investigate the inhibitory effect of landiolol and its metabolite M1 on the activity of multiple drug transporters such as P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, OAT1, and OAT3. Inhibition of the drug transporter(s) by landiolol and/or M1 metabolite may have an impact on the systemic exposure of concomitantly administered drug that are sensitive substrate(s) of these transporters. An *in vitro* drug interaction study will provide information on the potential of landiolol and M1 metabolite to inhibit these drug transporters and aid in determining the need for any in vivo drug-drug interaction study. A PMR was recommended to the Applicant to conduct an in vitro assessment to evaluate the potential of landiolol and its M1 metabolite to inhibit the following drug transporters: P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, multidrug and toxin extrusion (MATE) proteins (MATE1, MATE2-K), organic anion transporter (OAT)1, and OAT3. The Applicant has agreed to the PMR.

No clinical DDI studies have been conducted to evaluate the drug interaction liability of landiolol.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The to-be-marketed formulation, Landiolol HCl 300 mg for injection (LDLL300), is a sterile lyophilized powder of 280 mg of landiolol (equivalent to 300 mg of landiolol HCl), and an equal amount of mannitol (Table 3) in a single-dose vial to be reconstituted with 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for intravenous administration. Landiolol hydrochloride was originally developed by the Japan-based Ono Pharmaceutical Co., with the trade name Onoact® 50 for injection. Onoact is a lyophilized 50 mg formulation of Landiolol (ONO-1101). In addition to landiolol hydrochloride, the Onoact lyophilized

formulation contains only mannitol ([redacted] (b) (4)) in equal amounts (weight/weight) to the amount of landiolol hydrochloride and sodium [redacted] (b) (4) [redacted]. The Applicant started with this formulation and optimized the manufacturing process for stability and purity of the drug product without the need to change the drug product formulation (Table 2). The proposed to-be-marketed product contains the same excipients as the Onoact with the same ratio (w/w) of mannitol to landiolol. The formulation of the to-be-marketed product landiolol HCl 300 mg for injection is, except for the amount of active pharmaceutical ingredient, the same as the landiolol lyophilizate 600 mg formulation (Table 3)

Table 3. Formulations of applied Landiolol HCl 300 mg/600 mg for injection and Onoact® 50 mg.

Ingredients	Landiolol HCL 300 mg/600 mg for injection	Onoact® 50 mg
Landiolol HCl	300 mg/600 mg	50 mg
Mannitol	300 mg/600 mg	50 mg
Final concentration after reconstitution/dilution	6 mg/mL / 12 mg/mL	10 mg/mL

Note: Landiolol HCL 300 mg for injection is the to-be-marketed formulation.

Source: Table 5, page 11, 3.2.P.2 Pharmaceutical Development

The initial formulations developed by the applicant to support marketing applications in Europe included:

• Landiolol lyophilizate 600 mg (LDLL600)

• A liquid formulation containing 20 mg Landiolol, Landiolol concentrate 20 mg (LDL202).

• Landiolol lyophilizate 300 mg (LDLL300)

The Onoact, LDLL600, and LDL202 formulations were used in clinical PK and PD studies sponsored by the Applicant. The Applicant did not conduct a relative bioavailability study comparing Onoact® 50 mg and Landiolol HCl 300 mg formulations. Given the high water solubility of landiolol, relatively simple formulations, similar excipients and active to inactive ingredient ratio, significant differences in the bioavailability and are not expected for the parenteral solution intended solely for administration by intravenous injection.

Reference ID: 5161679

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Assays for landiolol and its metabolite M1 during development:

Landiolol and its metabolites M1/M2 in human blood were measured by LC-MS/MS methods to support pharmacokinetic measurement in all clinical studies. These bioanalytical methods used are adequately validated. The LC-MS/MS methods for quantification of the landiolol, M1, and M2 in human plasma were developed and validated at [redacted] (b) (4). The samples were prepared via protein precipitation. Detection was done by tandem mass spectrometry in the multiple reaction monitoring mode using the positive ion mode. The summary of LC-MS/MS methods performance is presented in Table 4.

Table 4. Summary review of LC-MS/MS methods measuring landiolol and its metabolites M1/M2 in human blood

Parameter	Landiolol	M1	M2
Validation assay range (ng/mL)	1.11-556	5.56-278	1.11-556
QCs (ng/mL)	2.79, 25.1, and 473	13.9, 125, and 236	2.78, 25.1, and 471
Recovery	99.9%	103.6%	97.0%
Inter-day precision (% CV)	5.04-6.02	4.29-5.48	3.59-7.26
Inter-day accuracy (%)	100.5-101.6	99.7-103.9	99.5-101.8
Intra-day precision (% CV)	2.41-6.81	3.08-6.71	3.12-8.92
Intra-day accuracy (%)	97.3-110	97.3-106.8	97.4-104.6
Selectivity	Landiolol, M1, and M2 of two sets (with and without internal standard) of selectivity samples taken from three different individuals (analyzed in duplicate) showed no interfering peaks in the areas of interest		
Freeze/thaw stability	3 freeze (-70°C)-thaw (ambient temperature) cycles		
Short term stability in precipitated human whole blood	23 hours at room temperature and at ice bath temperature		
Solvent stability	96 hours at room temperature and at nominal 2 to 8 °C		
Bench-top stability	2 hours at ambient temperature prior to preparation for analysis		
Processed stability	21 hours under auto-sampler conditions (about 5°C in a cooling tray)		
Long-term storage stability	449 days at nominal -20 °C and at nominal -70 to -85 °C		

Abbreviations: CV, coefficient of variation; QC, quality control.

Source: Method Validation Reports 52910, 841141, and 841141.

Reference ID: 5161679

4.2 Clinical Pharmacology Individual Study Review

4.2.1 *In vitro* Studies

Three *in vitro* studies with human biomaterials were conducted to determine the inhibitory effect of landiolol and its metabolite M1 on CYPs.

Studies 100058422 and 100059009

Aim of Study

The purpose of the two studies was to assess the potential of reversible inhibition of human CYP enzyme activities by landiolol and its metabolite M1 *in vitro*.

Experimental Design

Human liver microsomal preparations (0.1 mg/mL) were incubated with CYP specific probe substrates in the presence or absence of either landiolol (100 μM) or metabolite M1 (1300 μM) for 10 minutes at 37°C and the formation of the probe substrate metabolites determined by a validated HPLC-MS/MS analytical method. For those enzymes where the initial high concentration of the test drug showed relevant inhibition of enzyme activity, the assay was repeated by testing a lower drug concentration range of at least four different concentrations in the range of 1-100 μM (landiolol) or 30-1500 μM (M1) (Study 100059009).

Results

Landiolol did not appreciably inhibit CYP1A, CYP2C8, CYP2C9, or CYP3A (testosterone), the percentage of inhibition being below 10% at the 100 μM concentration. Some inhibition was detected for CYP2D6 (46.9%) and CYP3A (mizadolam; 34.6%), nevertheless, the IC_{50} for these CYP enzymes being >100 μM. CYP2C19 was inhibited by 70.3% at 100 μM and the IC_{50} value was subsequently determined at 69 μM. M1 did not appreciably inhibit CYP1A, CYP2C9, or CYP3A (testosterone), the percentage of inhibition being below 12% at 1300 μM. Some inhibition was detected for CYP2C8 (43.1%), CYP2D6 (55.3%) and CYP3A (mizadolam; 16.9%), nevertheless, the IC_{50} for these CYP enzyme being >1300 μM. CYP2C19 was inhibited by 59.1% at 1300 μM and the IC_{50} value was subsequently determined at 1300 μM.

Reviewer's comment: The clinically relevant concentration (unbound $C_{max,ss}$) was 3.12 μM based on the highest dose of 40 mcg/kg/min used in Study LDLL600.201) and the drug interaction index R_1 was calculated as 1.05. Given that the calculate R_1 is close to cut-off value (1.02) and landiolol with short elimination $t_{1/2}$ (3.0-4.5 min) is used for single iv infusion up to 24 hours, landiolol is not likely to exert inhibitory effect on CYP2C19 activity in vivo.

Reference ID: 5161679

Study 100059780

Aim of Study

The purpose of this study was to assess the potential of time-dependent inhibition of human CYP enzyme activities by landiolol and its metabolite M1 *in vitro*.

Experimental Design

Human liver microsomal preparations (0.1 mg/mL) were preincubated with either landiolol (100 μM) or metabolite M1 (1300 μM) in the absence or presence of an NADPH-generating system for 30 minutes. CYP specific probe substrates were added to the mixture and incubated for another 10 minutes at 37°C. The formation of the probe substrate metabolites was determined by a validated HPLC-MS/MS analytical method. Time-dependent CYP inhibition by either landiolol or metabolite M1 was evident if the mean % inhibition value from samples preincubated without NADPH was lower than from samples preincubated with NADPH.

Results

Landiolol did not elicit time-dependent inhibition of CYP2C9, CYP2C19 or CYP3A, with % inhibition values of -1.7%, -2.5% and 1.3% in the presence of NADPH compared to 21.6%, 8.3% and 4.5%, respectively, in the absence of NADPH. Time-dependent inhibition was detected for CYP1A and CYP2D6 with % inhibition values of 21.0% and 54.9% in the presence of NADPH compared to -3.8% and 12.4%, respectively, in the absence of NADPH at a concentration of 100 μM. Metabolite M1 did not elicit time-dependent inhibition of CYP2C9, CYP2C19 or CYP3A, with % inhibition values of 6.6%, 1.6% and 2.6% in the presence of NADPH compared to 14.2%, 9.4% and 4.8%, respectively, when incubated without NADPH. Some inhibition was detected for CYP1A and CYP2D6 with 14.5% and 51.5% in the presence of NADPH, compared to -5.1% and 12.4%, respectively, when incubated without NADPH at a concentration of 1300 μM.

Reviewer's comment: Given that landiolol showed 54.9% inhibition at super-therapeutically relevant concentrations (100 μM) and landiolol is used for single iv infusion up to 24 hours, landiolol and M1 is not likely to exert time-dependent inhibitory effect on CYP2D6 activity in vivo.

Reference ID: 5161679

4.2.2 In vivo Studies

Study CPA368-10

A prospective, randomized, double blinded, crossover, two-treatment, two-sequence, short-term pharmacokinetic, pharmacodynamic and tolerability, single center study to compare AOP200704 (Onoact® 50) vs. esmolol in healthy subjects.

Objectives

The objectives of the study were to assess the short-term PK, PD and tolerability of landiolol (Onoact® 50) compared to esmolol in Caucasians.

Study design

Adult Caucasian healthy subjects, male or female, aged 18 to 45 years, with a body weight of 50-90 kg and a body mass index (BMI) of 18.5-30.0 kg/m^2 were enrolled in the study. It was a double-blind, 2-treatment, 2-sequence, cross-over study with landiolol (Onoact) and esmolol (Brevibloc), conducted at a single study center. In order to simulate adrenergic stimulation with the associated hemodynamic response, subjects were administered dobutamine at a stable dose for at least 20 min before and during the administration of study drugs, and after discontinuation of study drugs until the HR for any given subject had returned to the values before study drug administration. Dobutamine was titrated for a targeted HR increase of at least 30 bpm versus baseline (maximum dose: 30 μg/kg/min) with an initial dose of 10 μg/kg/min for 10 min.

Subjects were randomized in a 1:1 ratio to sequentially receive landiolol (Onoact, test) and esmolol (Brevibloc, reference) or vice versa. Landiolol (Onoact) was administered as an iv infusion at a dose of 10 μg/kg/min for 60 min. Esmolol was administered as an iv infusion at a dose of 50 μg/kg/min for 60 min. Study drugs were administered on the morning of Day 1 of each study period; the duration of each study period was 2 days. The wash-out phase between treatments was at least 2 days. In case treatment with study drug failed to decrease the dobutamine induced HR increase by 20 bpm by 40 min, the rate of infusion of landiolol and/or esmolol was planned to be doubled for the next 60 min. Blood samples were collected at scheduled intervals in each study period. Blood concentrations of landiolol, esmolol and their metabolites were determined and the pharmacokinetic parameters C_{max}, concentration at steady state (C_{ss}), C1h, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, residual area, terminal elimination rate constant (λz), $t_{1/2}$, CL and Vd were calculated using a non-compartmental model. Hemodynamic assessments

Reference ID: 5161679

included the mean dose necessary to suppress the dobutamine-induced increase in HR, dose/effect relation, time until a decrease of 10 bpm, 20 bpm and the maximum effect, mean time to recovery by 10 and 20 bpm, time to reach maximum HR after discontinuation of infusion, and blood. Safety and tolerability assessments included AEs, clinical laboratory examination, physical examination, ECG and vital signs, and signs and symptoms of inflammation at the site of administration

Results

The mean concentration time profiles of landiolol and esmolol are presented in Figure 1. PK parameters, based on a non-compartmental model, are summarized in Table 5. Maximum blood concentrations were higher for landiolol than for esmolol with arithmetic means of 191 and 162 ng/mL, respectively, and were reached at 36 and 24 min for landiolol and esmolol, respectively. In most subjects, only a monophasic elimination phase was observed. The mean $t_{1/2}$ was similar for landiolol and esmolol (3.5 and 3.7 min, respectively). Clearance and Vd were higher for esmolol than for landiolol. The concentration profile of landiolol showed less fluctuation during the infusion compared to esmolol. Mean HR profiles are shown together with blood concentration profiles of landiolol or esmolol in Figure 2. Elevated HR due to dobutamine stimulation were decreasing continuously during infusion of landiolol (Onoact) or esmolol and showed a clear inverse relationship between beta-blocker concentration and HR.

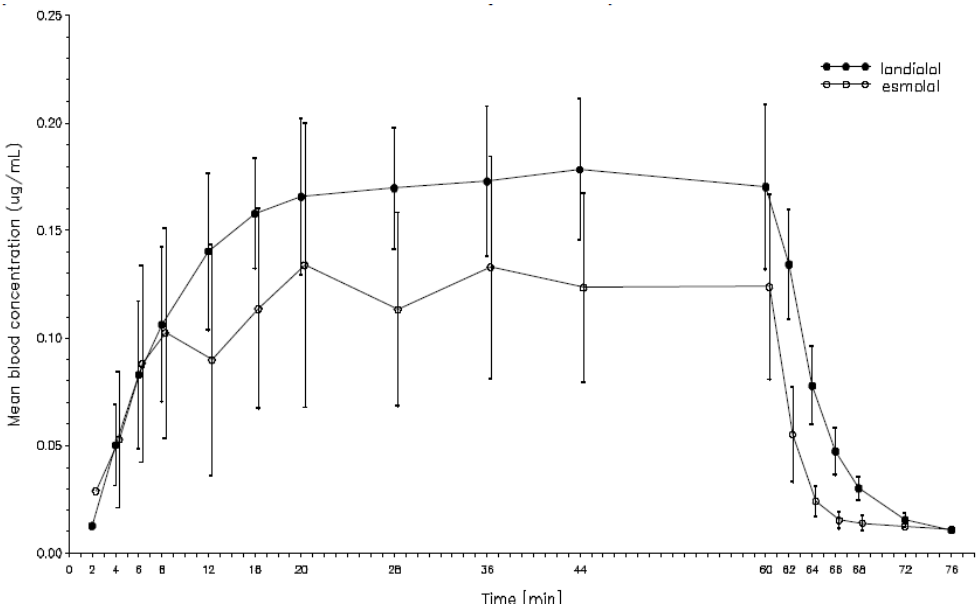


Figure 1. Study CPA368-10 Mean (±SD) Blood Concentration Time Profiles of Landiolol and Esmolol (PK population)

Standard deviation is presented for timepoints with more than 5 measurable concentrations. PK=pharmacokinetics, SD=standard deviation.

Source: Figure 11.4-1.1, page 56, CPA368-10 CSR

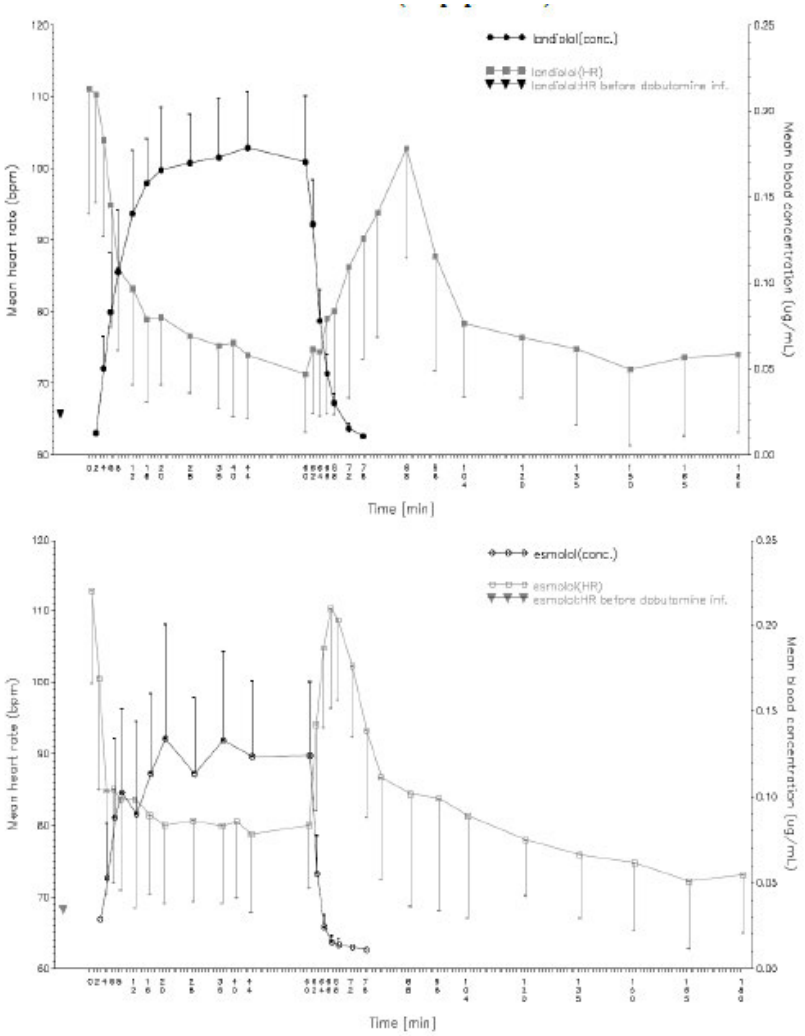
Table 5. Study CPA368-10 Mean (±SD) Pharmacokinetic Parameters of Landiolol and Esmolol (PK population)

PK Parameter	Treatment	
	Landiolol (Onoact) N=16	**Esmolol N=16**
C_{max} (ng/mL)	191 (37) (n=16)	162 (64) (n=16)
$AUC_{0-\infty}$ (ng.h/mL)	164 (28) (n=16)	118 (42) (n=15)
$t_{1/2}$ (min)	3.5 (0.5) (n=16)	3.7 (4.0) (n=15)
t_{max} (min)	36.0 (15.2) (n=16)	23.9 (12.6) (n=16)
CL (mL/kg.min)	62.6 (9.4) (n=16)	482 (187) (n=15)
Vd (mL/kg)	317 (78) (n=16)	2221 (1645) (n=15)

$AUC_{0-\infty}$=area under the concentration curve from time zero to infinity, CL=clearance, C_{max}=maximum concentration, N=number of subjects, n=number of subjects with data available, PK=pharmacokinetic, SD=standard deviation, $t_{1/2}$=half-life, t_{max}= time to C_{max}, Vd=volume of distribution.

Source: Table 14.2.2, page 184, CPA368-10 CSR

Reference ID: 5161679



Study drug was infused during 60 min (to all subjects). The infusion of dobutamine lasted until the heart rate returned to the value before study drug infusion. It is individual for each subject and period. Standard deviation is presented for timepoints with more than 5 measurable concentrations.
PD=pharmacodynamic, SD=standard deviation

Figure 2. Study CPA368-10 Mean (±SD) Heart Rate and Landiolol and Esmolol Blood Concentration Time Profiles.

Source: Figure 11.4-1.3.3 and Figure 11.4-1.3.4, page 93-95, CPA368-10 CSR.

Study CPA410-12

A single center prospective, randomized, double-blind, cross-over, three-treatment periods, pharmacokinetic, pharmacodynamic, safety and tolerability study to compare bolus

Reference ID: 5161679

administration of AOP LDL202, ONO LDL50 (Onoact® 50) and esmolol in healthy volunteers after a pilot phase of AOP LDL202 safety and local tolerability assessment.

Objectives

The objectives of the study were to assess the safety and local tolerability of the highest landiolol concentrate 20 mg (LDL202) dose (pilot phase), and to compare the short-term PK, hemodynamics (PD), and safety of landiolol concentrate 20 mg (LDL202), Onoact® 50, and esmolol in Caucasian subjects (main phase).

Study design

Adult Caucasian healthy subjects, male or female, aged 18 to 45 years, with a body weight of 50-90 kg and a body mass index (BMI) of 18.5-30.0 kg/m^2 were enrolled in the study. The study was a double-blind, 3-period, cross-over study with landiolol concentrate 20 mg (LDL202), landiolol (Onoact), and esmolol (Brevibloc), conducted at a single study center. The study consisted of a pilot and a main phase. In the pilot phase of the study (N=3), landiolol concentrate 20 mg (LDL202) or placebo (saline) were administered as a single bolus dose. Landiolol concentrate 20 mg (LDL202) was administered as iv bolus infusion at a dose of 300 μg/kg.

In the main phase (N=12), increasing bolus doses of study drugs were administered:

- Landiolol concentrate 20 mg (LDL202): bolus doses of 100 μg/kg, 200 μg/kg, 300 μg/kg in 1-hour intervals
- Onoact 50: bolus doses of 100 μg/kg, 200 μg/kg, 300 μg/kg in 1-hour intervals
- Esmolol: bolus doses of 500 μg/kg, 1000 μg/kg, 1500 μg/kg in 1-hour intervals

In the main phase, subjects were randomized to 1 of 6 treatment sequences, and sequentially received the 3 study drugs in 3 study periods, i.e., each subject received 9 doses of study drugs in total. Study drugs were administered on the morning of Day 1 of each study period; the duration of each study period was 2 days. The wash-out phase between treatments was at least 2 days. Blood concentrations of landiolol, esmolol and their metabolites were determined and the PK parameters C_{max}, time to Cmax (t_{max}), lag time, i.e., the time prior to the first measurable (non-zero) concentration (tlag), AUC_{0-t}, $AUC_{0-\infty}$, residual area, λz, $t_{1/2}$, CL and Vd were calculated. Hemodynamic assessments included blood pressure, HR, and ECG parameters. Safety and

Reference ID: 5161679

tolerability assessments included AEs, clinical laboratory examination, physical examination, blood pressure, HR, ECG, and signs and symptoms of inflammation at the site of administration.

Results

Blood concentration profiles of landiolol concentrate 20 mg (LDL202), Onoact, and esmolol are presented in Figure 3. PK parameters, based on a non-compartmental model, are summarized for landiolol concentrate and Onoact in Table 6. The PK parameters Cmax and AUC values were very similar for landiolol concentrate 20 mg (LDL202) and Onoact. For both, dose-proportional increases in Cmax and AUC were observed. The results for other PK parameters were similar for landiolol concentrate 20 mg (LDL202) and Onoact. Tmax appeared to be independent of the dose. Mean blood pressure and HR profiles are shown along with blood concentration profiles in Figure 4. Decreases in HR were observed with landiolol concentrate 20 mg (LDL202) and Onoact at all doses studied, whereas only a minor effect of esmolol on HR was observed.

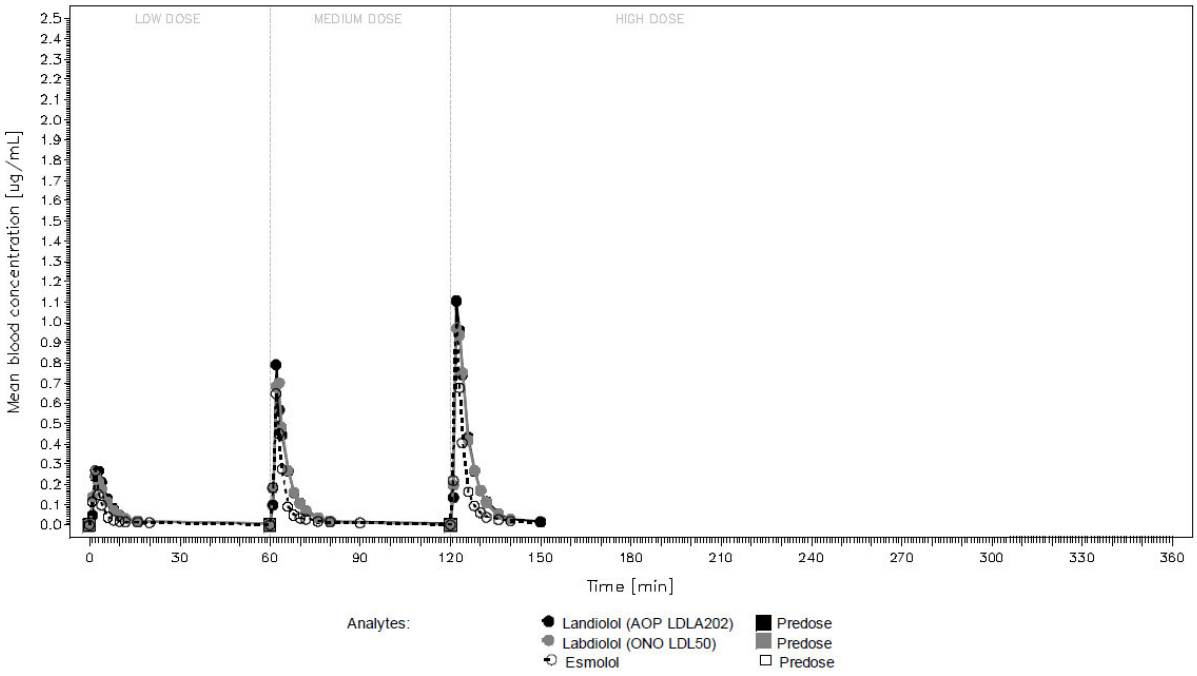


Figure 3. Study CPA410-12 Mean Blood Concentration Profiles of Landiolol Concentrate 20 mg (LDL202), Onoact, and Esmolol (PK population)

Source: Figure 11.4.1-1.1.1, page 69, CPA410-12 CSR.

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Table 6. Study CPA410-12 Mean (±SD) Pharmacokinetic Parameters of Landiolol (Landiolol concentrate 20 mg [LDL202]) versus Onoact [PK population])

PK Parameter	Treatment Group and Landiolol Dose					
	LDL202 (landiolol concentrate)			Onoact		
	0.1 mg/kg N=12	0.2 mg/kg N=12	0.3 mg/kg N=12	0.1 mg/kg N=12	0.2 mg/kg N=12	0.3 mg/kg N=12
C_{max} (ng/mL)	294 (1509)	788 (1501)	1143 (1662)	264 (1772)	791 (1421)	1055 (1675)
$AUC_{0-\infty}$ (ng.h/mL)	25 (1293)	58 (1247)	92 (1346)	23 (1399)	62 (1231)	89 (1364)
$t_{1/2}$ (min)	3.2 (1.2)	3.4 (1.1)	3.6 (1.1)	3.0 (1.1)	3.4 (1.1)	3.6 (1.1)
t_{max} (min)	3.0 (1.8, 4.2)	1.8 (1.8, 4.2)	1.8 (1.8, 3.0)	1.8 (1.2, 4.2)	3.0 (1.2, 4.2)	2.4 (1.8, 4.2)
CL (mL/kg.min)	66.1 (1.3)	57.3 (1.3)	54.1 (1.4)	74.0 (1.4)	54.1 (1.2)	55.9 (1.4)
Vd (mL/kg)	305.4 (1.4)	283.8 (1.2)	283.4 (1.4)	323.4 (1.4)	267.7 (1.3)	294.1 (1.4)

Geometric mean (geometric SD) are presented for all values, except for t_{max} which is presented as median (range).
$AUC_{0-\infty}$=area under the concentration curve from time zero to infinity, CL=clearance, C_{max}=maximum concentration, N=number of subjects, PK=pharmacokinetic, SD=standard deviation, $t_{1/2}$ =half-life, t_{max}=time to C_{max}, Vd=volume of distribution.

Source: Table 11.4.1-1.1 and 11.4.1-1.2, page 77-78CPA410-12 CSR

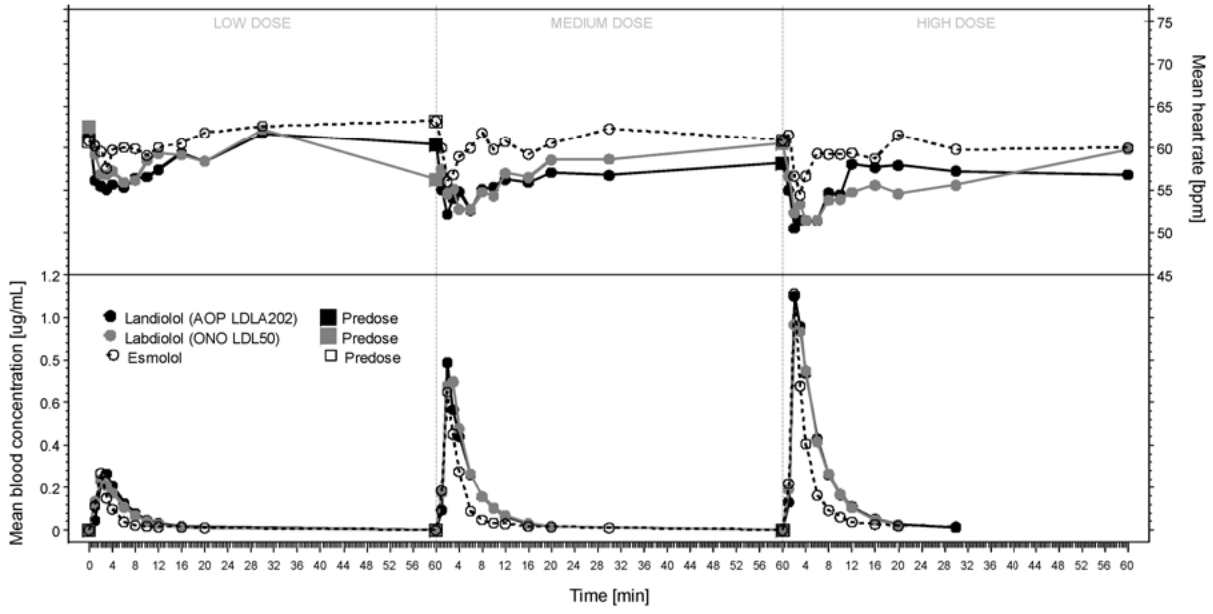


Figure 4. Study CPA410-12 Treatment Period Mean Systolic and Diastolic Blood Pressure, Heart Rate and Blood Concentration Time Profiles of Landiolol Concentrate 20 mg (LDL202), Onoact, and Esmolol.

Source: Figures 11.4.1-3.1.2, 11.4.1-3.2.2, and 11.4.1-3.3.2, pages 130-134, CPA410-12 CSR.

Reference ID: 5161679

Study CPA422-12

A single-center prospective, randomized, double-blind, cross-over, pharmacokinetic, safety and tolerability study to compare long-term infusion administration of LDLL600 against esmolol in healthy volunteers.

Objectives

The objectives of the study were to assess the long-term PK, hemodynamic (PD), safety and tolerability of landiolol lyophilizate 600 mg (LDLL600) and esmolol in Caucasian subjects.

Study design

Adult Caucasian healthy subjects, male or female, aged 18 to 45 years, with a body weight of 50-90 kg and a body mass index (BMI) of 18.5-30.0 kg/m^2 were enrolled in the study. The study was a double-blind, randomized, double-blind, 2-period, cross-over study, conducted at a single study center. Subjects were randomized in a 1:1 ratio to sequentially receive landiolol lyophilizate 600 mg (LDLL600) and esmolol (Brevibloc 10 mg/mL) or vice versa. Landiolol lyophilizate 600 mg (LDLL600) was administered as an i.v. infusion at a dose of 10 μg/kg/min for 2 hours, followed by 20 μg/kg/min for 2 hours, and 40 μg/kg/min for 20 hours. Esmolol was administered as an i.v. infusion, at a dose of 50 μg/kg/min for 2 hours, followed by 100 μg/kg/min for 2 hours, and 200 μg/kg/min for 20 hours. Subjects were treated in a cross-over design with landiolol and esmolol, the duration of each study period being 3 days. The wash-out phase between treatments was at least 2 days. Blood concentrations of landiolol, esmolol and their metabolites were determined and the pharmacokinetic parameters Cmax, tmax, AUC0-t, AUC0-∞, residual area, λz, $t_{1/2}$, CL and Vd were calculated, based on non-compartmental analysis. Hemodynamic assessments included blood pressure, HR, and ECG parameters. Safety and tolerability assessments included AEs, clinical laboratory examination, physical examination, blood pressure, HR, ECG, and signs and symptoms of inflammation at the site of administration.

Results

Mean concentration time profiles of landiolol (LDLL600) and esmolol are presented in Figure 5. Mean blood concentrations increased with every dose increase for both study drugs. The blood concentrations of esmolol were somewhat higher than those of landiolol at every dose level. The mean blood concentration profile from 6 until 24 hours after the start of the infusion showed less

Reference ID: 5161679

variation for landiolol than for esmolol. After termination of the infusion, the parent drugs rapidly disappeared from the blood. PK parameters, based on a non-compartmental model, are summarized in Table 7.

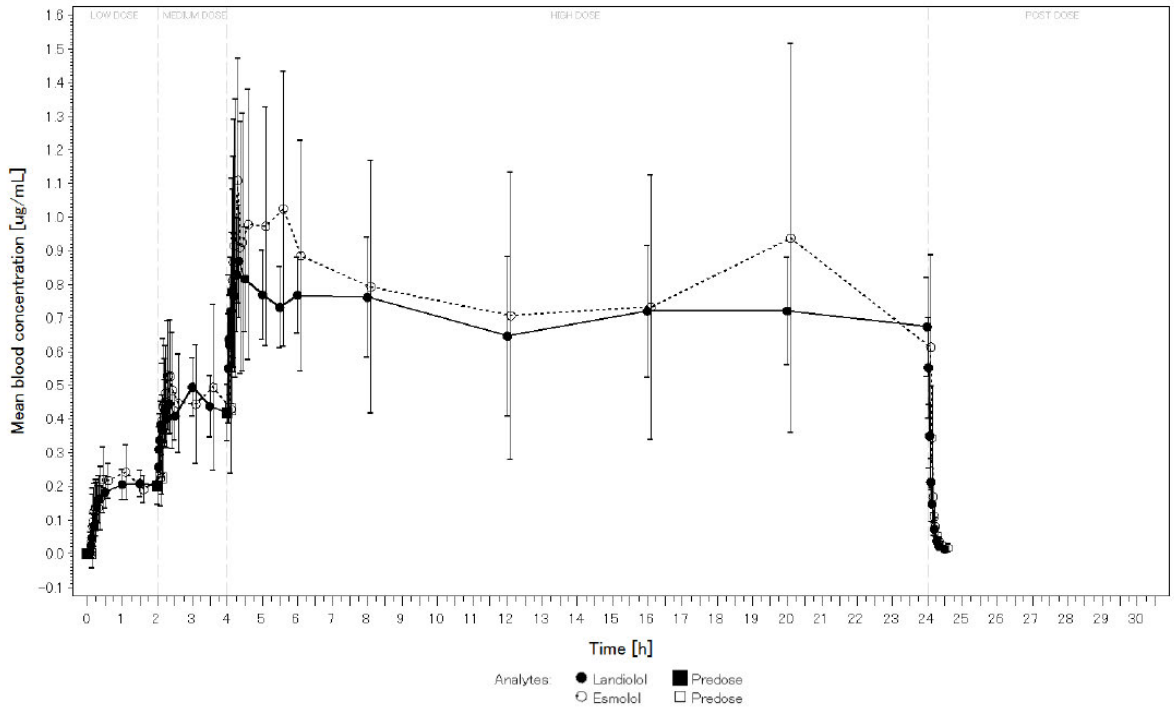


Figure 5. Study CPA422-12 Mean (±SD) Concentration Time Profiles of Landiolol (LDLL600) and Esmolol (PK population)

Source: Figure 11.4.1-2.1.1. page 73, CPA422-12 CSR.

Table 7. Study CPA422-12 Mean (±SD) Pharmacokinetic Parameters of Landiolol (LDLL600) and Esmolol (PK population)

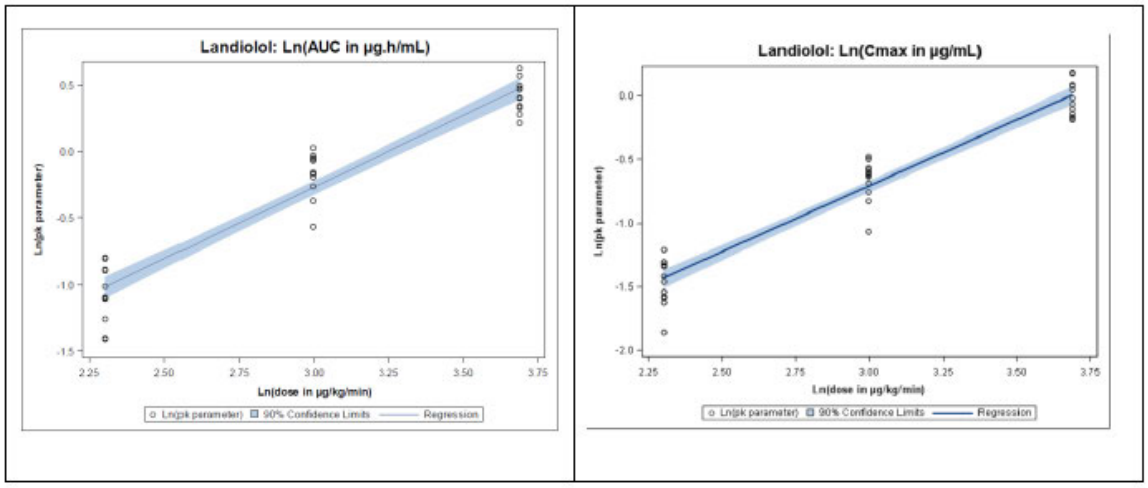
PK Parameter	Treatment	
	LDLL600 N=12	**Esmolol N=12**
C_{max} (ng/mL)	1003 (1142)	1362 (1294)
$AUC_{0-\infty}$ (ng.h/mL)	15331 (1185)	15987 (1542)
$t_{1/2}$ (min)	4.5 (1.2)	6.9 (1.5)
t_{max} (h)	4.5 (4.2, 16.0)	4.8 (4.1, 20.0)
CL (mL/kg.min)	56.1 (1.2)	269.0 (1.5)
Vd (mL/kg)	365.8 (1.2)	2670.8 (1.7)

Geometric mean (geometric SD) are presented for all values, except for t_{max} which is presented as median (range). $AUC_{0-\infty}$=area under the concentration curve from time zero to infinity, CL=clearance, C_{max}=maximum concentration, N=number of subjects, PK=pharmacokinetic, SD=standard deviation, $t_{1/2}$ =half-life, t_{max}=time to C_{max}, Vd=volume of distribution.

Source: Tables 11.4.1-1.1 and 11.4.1-1.2, pages 83-92, CPA422-12 CSR.

Reference ID: 5161679

An additional statistical analysis was conducted to investigate dose-proportionality for landiolol using a power model. Dose proportionality was confirmed for AUC and C_{max} (Figure 6). Further statistical analysis demonstrated a statistically significant dose proportionality across all dose ranges ($p<0.0001$, refer to Table 8). Specifically, dose proportionality was demonstrated using a 90% confidence interval for the slope, and as calculated by a power model, results are within dose-proportionality limits (dose-proportionality limits were set as (1+log(0.8)/(log(high dose/low dose), 1+log(1.25)/log(high dose/low dose).



Notes: Axes are designated as follows: x-axis, both panels: ln(landiol dose in µg/kg/min); y-axis, left panel: ln(AUC in µg*h/mL), right panel: ln(C_{max} in µg/mL). Shading indicates 90% confidence limits of the regression line.

Figure 6. Study CPA42-12 Dose Proportionality Analysis of Landiolol (LDLL600)

Source: Figure 8, page 36, Clinical pharmacology summary.

Table 8. Study CPA422-12 Summary of Statistical Analysis of Dose Proportionality of Landiolol (10, 20 and 40 µg/kg/min)

Effect		Estimate	Standard error	Limits for dose proportionality: (1+log(0.8)/(log(high dose/low dose), 1+log(1.25)/log(high dose/low dose)	p-value (for testing difference from 0)
Landiolol:				90% CI within limits:	<.0001
Ln(AUC in µg.h/mL)	Ln(dose in µg/kg/min)	1.0747 (90% CI: 1.0014 , 1.1480)	0.04277	0.8390 , 1.1610	
Landiolol:				90% CI within limits:	<.0001
Ln(Cmax in µg/mL)	Ln(dose in µg/kg/min)	1.0371 (90% CI: 0.9780 , 1.0963)	0.03453	0.8390 , 1.1610	

AUC=area under the curve; CI=confidence interval; C_{max}=maximal concentration; Ln=natural logarithm

Source: Table 10, page 36, Clinical pharmacology summary.

Reference ID: 5161679

Mean blood pressure and HR profiles are shown together with blood concentration profiles of landiolol and esmolol in Figure 7. Approximately 1 hour after the start of the high dose, the HR profiles of both treatments show an increasing trend despite the high landiolol and esmolol concentrations. This trend coincides with serving lunch to the subjects, thus reflecting a period of higher activity.

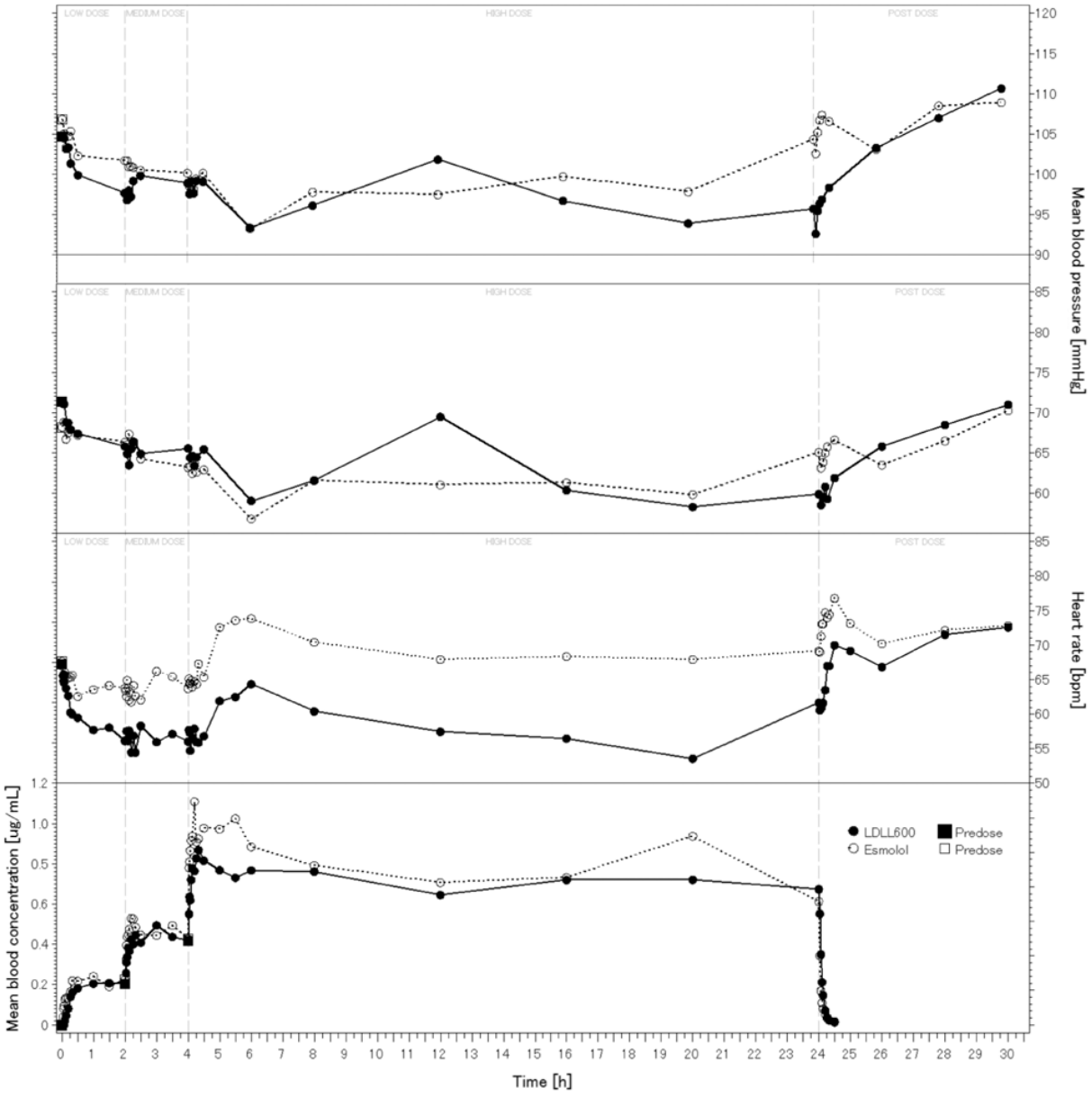


Figure 7. Study CPA422-12 Treatment Period Mean Systolic and Diastolic Blood Pressure, Heart Rate and Blood Concentration Time Profiles of Landiolol (LDLL600) and Esmolol

Source: Figures 11.4.1-3.1.1, 11.4.1-3.2.1, 11.4.1-3.3.1. pages 106-111, CPA422-12 CSR.

Reference ID: 5161679

Study LDLL600.201

Open-label two-arm PD and PK study of landiolol in patients with tachycardic atrial fibrillation or atrial flutter.

Objectives

The objectives of the study were to study the hemodynamics/pharmacodynamics, PK, tolerability, and safety of landiolol (LDLL600) in Caucasian patients with tachycardic atrial fibrillation or atrial flutter treated either with a bolus + maintenance infusion (bolus dosing scheme) or a maintenance infusion only (alternative dosing scheme).

Study design

Adult patients with atrial fibrillation or atrial flutter and a ventricular rate between 100 and 200 bpm, clinical symptoms (including but not limited to palpitations, irregular pulse, fatigue, rapid heartbeat, shortness of breath, dizziness, sweating), and SBP ≥100 mmHg were enrolled in the study. The study was an open-label, randomized, parallel, 2-arm study, conducted at a single study center. Patients were randomized 1:1 to the bolus + maintenance or the maintenance only dosing scheme with landiolol. Patients in the bolus + maintenance dosing scheme received a bolus infusion of 100 μg/kg/min landiolol for 1 minute, followed by continuous i.v. infusion of 40 μg/kg/min; the maximal total treatment duration was 211 min. Patients in the maintenance only dosing scheme received a continuous i.v. infusion of 40 μg/kg/min landiolol; the maximal total treatment duration was 210 min. If successful HR control (defined as HR < 90 bpm or ≥ 20% reduction of HR from baseline) was achieved within 16 min (approximately 4 times the half-life of landiolol) of continuous infusion, dosing continued with 40 μg/kg/min or could be reduced by 50% if considered sufficient to maintain HR control. If successful HR control was not achieved after 16 min continuous infusion, the dose was increased to 80 μg/kg/min. If successful HR control was not achieved 30 min after landiolol continuous infusion start, a switch to rescue treatment (esmolol, metoprolol, amiodarone, verapamil, digoxin or electric cardioversion) was allowed and the landiolol infusion was stopped. At any time between 0 and 180 min, if successful HR control and conversion to sinus rhythm were achieved, the landiolol dose was to continue for another 10 min after conversion to sinus rhythm and then the landiolol infusion was to be stopped. At 180 min after landiolol continuous infusion start a switch phase to oral therapy was started. Administration of oral agents at minute 180 was followed by a reduction of the landiolol dose to 50% at minute 190 and termination at minute 210.

Blood concentrations of landiolol and metabolites (M1 and M2) were measured. The PK parameters Cmax, tmax, AUC0-t, AUC0-∞, residual area, λz, t1/2, CL and Vd were determined

Reference ID: 5161679

Results

Mean concentration time profiles of landiolol with the 2 dosing schemes are presented in Figure 8. With both dosing schemes, landiolol concentrations increased rapidly after start of infusion; the increase was more pronounced with the bolus dosing regimen. After bolus + maintenance dosing, stable concentrations were observed between 60 and 190 min post-dose, while after maintenance only dosing, concentrations were stable between 30 and 190 min post-dose. When dose changes were corrected to a standard dose it became apparent that both dosing schemes provided stable blood concentrations of landiolol by 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 summarized in Table 9.

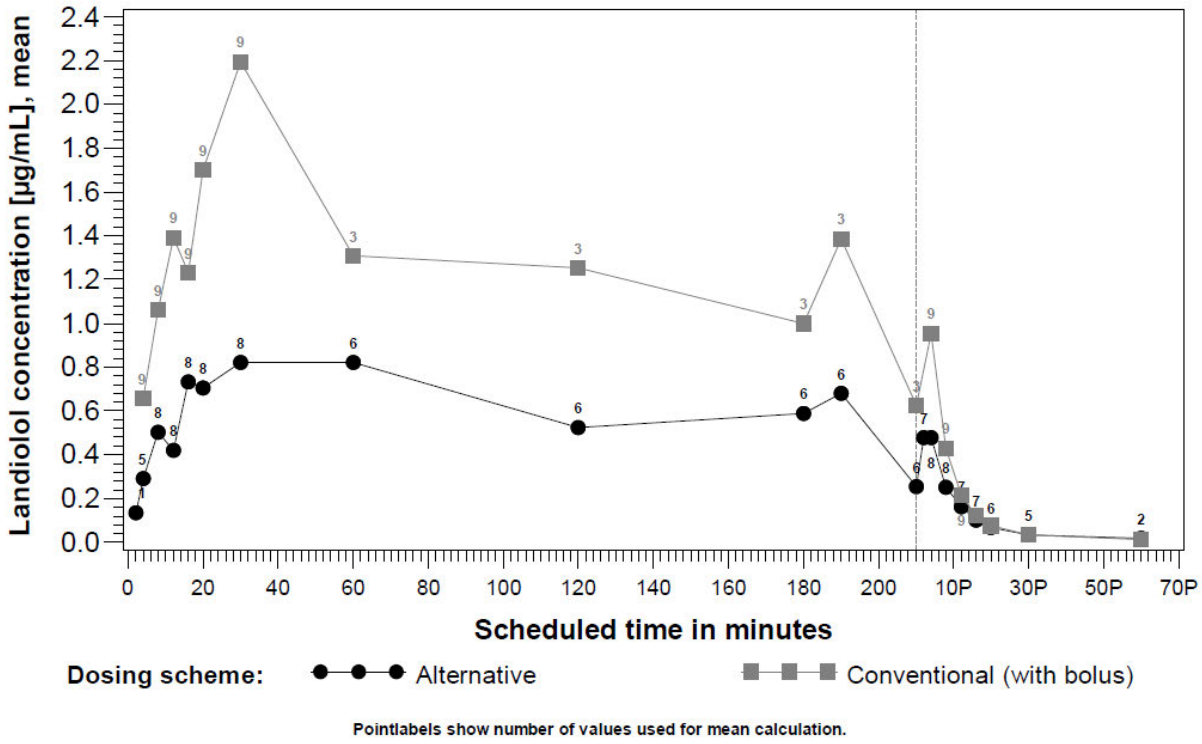


Figure 8. Study LDLL600.201 Mean Concentration Time Profiles of Landiolol (Bolus + Maintenance versus Maintenance Only Dosing Scheme).

Source: Figure 14.2.4-3.9.2.1. page 795, LDLL600.201 CSR

Reference ID: 5161679

Table 9. Study LDLL600.201 Mean (±SD) Pharmacokinetic Parameters of Landiolol Continuous Infusion With and Without a Preceding Landiolol Bolus.

PK Parameter	Treatment Group	
	Landiolol (bolus + maintenance dosing) N=9	**Landiolol (maintenance only dosing) N=8**
C_{max} (ng/mL)	2247 (779)	1121 (511)
$AUC_{0-\infty}$ (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 t_{max} which is presented as median (range).
$AUC_{0-\infty}$=area under the concentration curve from time zero to infinity, CL=clearance, C_{max}=maximum concentration, N=number of subjects, SD=standard deviation, $t_{1/2}$ =half-life, t_{max}=time to C_{max}, Vd=volume of distribution.

Source: Table 14.2.5-1.2.1, pages 979-984, LDLL600.201 CSR.

Figure 9 summarizes the profile of the heart rate changes and includes the heart rate profile immediately after the landiolol treatment period ended, the latter separated between patients that did versus patients that did not meet the HR reduction threshold criteria. Analysis of HR, SBP and DBP showed no significant difference between the 2 dosing schemes (FAS population). Onset of the HR lowering effect was already observed in the maintenance only group after 2 minutes (no assessment in the bolus + maintenance group). In both dosing schemes HR was reduced 4 min after initiation of continuous administration from the baseline mean value of 125.0 bpm to 113.0 bpm (-9.6%), and further to 103.8 bpm (-17.0%) after 16 min. Mean HR further decreased to 101.5 bpm (-18.8%) at 30 min and 94.2 bpm (-24.6%) at 60 min. Patients with successful HR control achieved and maintained during the first 16 min after continuous landiolol infusion start (primary endpoint): The frequency of patients with successful HR control was 50% for the overall analysis set (60.0% and 40.0% in the maintenance only and the bolus + maintenance dosing scheme, respectively).

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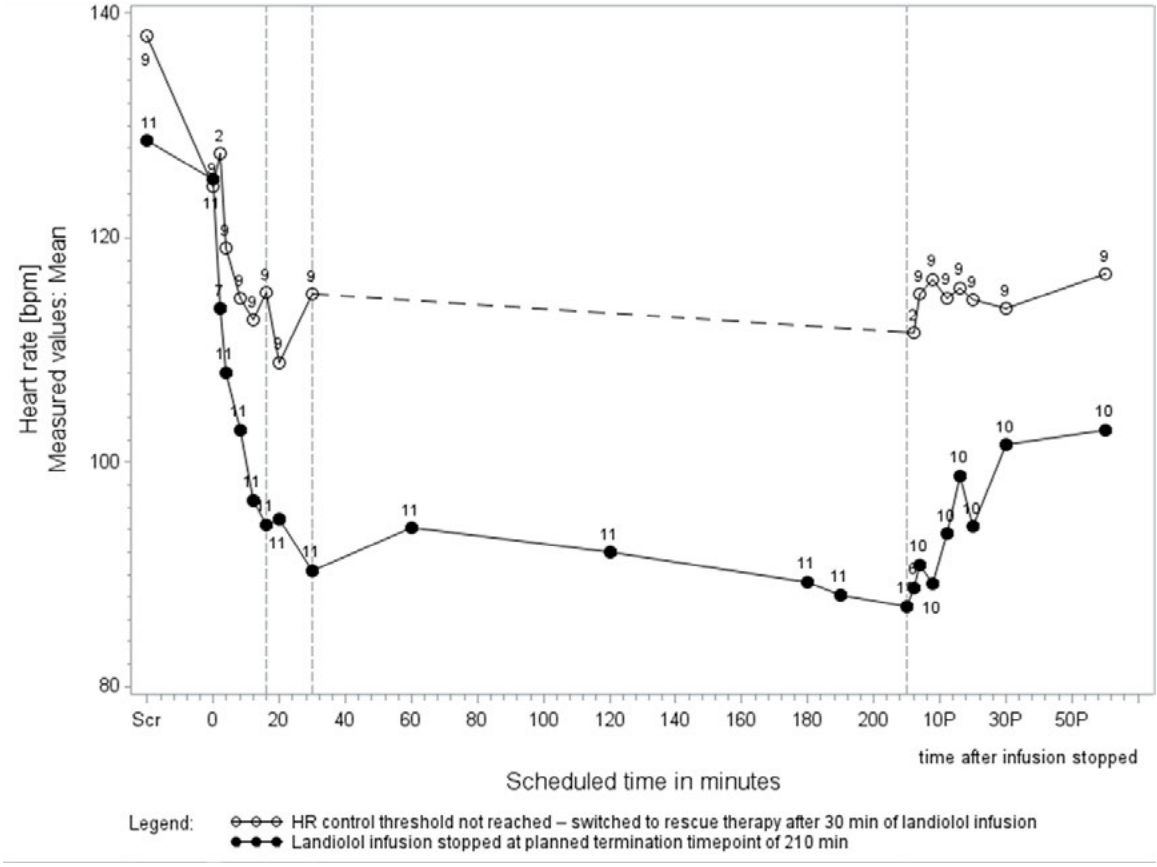

Figure 9. Mean Heart Rate Profiles of Patients (n=20) with Atrial Fibrillation or Atrial Flutter Treated with Landiolol (numbers for each point represent number of patients)

Source: Figure 11, page 44, Clinical pharmacology summary.

Reference ID: 5161679

Influence of Hepatic Impairment on the Pharmacokinetics and Pharmacodynamics of Landiolol hydrochloride, an Ultra-Short-Acting β1 Blocker

Publication: Takenori Takahata, Norio Yasui-Furukori, Juichi Sakamoto, Koji Suto, Toshiyuki Suto, Tomonori Tateishi, and Akihiro Munakata, Drugs R D 2005; 6 (6): 385-394.

Study Objective: The study objective was to investigate the impact of mild to moderate hepatic impairment on the PK and hemodynamics (PD) of landiolol.

Study Design: Prospective, uncontrolled, single-center, open-label, parallel-group study with Onoact. Landiolol was administered as a bolus/infusion regimen, with 1-min i.v. administration of 60 μg/kg, followed by continuous infusion at 20 μg/kg/min for 60 min.

Study Population: 6 patients with hepatic impairment (5 patients with Child Pugh Class A and 1 patient with Child Pugh Class B), and 6 healthy subjects. Mean age was 65 and 63 years in patients with hepatic impairment and healthy subjects, respectively.

Pharmacokinetic Assessments: PK of landiolol and its main M1 metabolite was assessed in blood and urine during and up to 24 hours after the start of administration.

Bioanalysis: Blood and urine concentrations of landiolol hydrochloride and its major metabolite M-1 were quantified by high-performance liquid chromatography (HPLC), as outlined below. Initially, landiolol hydrochloride and M-1 were extracted from blood in ethanol. The supernatant was then evaporated. The blood sample residues and urine samples were extracted by C18 solid-phase extraction (SPE). The eluent was extracted with ethyl acetate under mild alkaline conditions. The organic layer contained landiolol hydrochloride, while the aqueous layer contained the M-1 metabolite. After evaporation of the organic layer, the residue was reconstituted with the mobile phase and injected into the HPLC-UV system. The aqueous layer was applied to a C18 SPE column; the resulting eluate was evaporated. The residue was reconstituted with the mobile phase and injected into the HPLC-UV system. The quantitative ranges for landiolol hydrochloride and M-1 concentrations in the blood were between 0.05–10 and 0.1–20 μg/mL, respectively. The quantitative ranges of landiolol hydrochloride and M-1 in urine samples were between 0.5–25 and 2.5–100 μg/mL, respectively. These methods were validated for accuracy, precision, sensitivity and specificity.

Pharmacokinetic Results: PK parameters, based on non-compartmental analysis, are summarized in Table 10.

Reference ID: 5161679

Table 10. Mean (±SD) Pharmacokinetic Parameters of Landiolol in Patients with Hepatic Impairment versus Healthy Subjects.

PK Parameter	Treatment Group		p-value*
	Adult Patients with Hepatic Impairment N=6	Healthy Adults N=6	
C_{max} (ng/mL)	942 (140)	665 (119)	0.004
$C_{61\ min}$ (ng/mL)	866 (54)	641 (125)	0.002
t1/2 (min)	4.0 (0.4)	4.0 (1.5)	0.993
$AUC_{0-\infty}$ (min*ng/mL)	52400 (5200)	36300 (3600)	<0.001
CL (min*mL/kg)	24.2 (2.4)	35.0 (3.8)	<0.001
Vd (mL/kg)	141 (26)	202 (79)	0.103

$AUC_{0-\infty}$=area under the concentration curve from time zero to infinity, CL=clearance, C_{max}=maximum concentration, C_{61min}=concentration at 61 min after start of administration, N=number of subjects, SD=standard deviation, $t_{1/2}$=half-life, Vd=volume of distribution.
* determined by Student's t-test.

Mean serum cholinesterase levels were lower in patients with hepatic impairment compared to healthy subjects (-62%). Blood concentrations of landiolol were higher in patients with hepatic impairment (increase in geometric mean Cmax and AUC0-∞ values in patients compared to healthy subjects of +42% and +44%, respectively). T1/2 was not different from healthy subjects despite lower mean CL due to a parallel decrease in Vd and CL. This finding could be a result of the lower mean serum cholinesterase levels in hepatically impaired subjects as well as other factors. The AUC0-∞ for M1 was significantly increased in patients with hepatic impairment compared to healthy volunteers, whereas there was no significant difference in Cmax or t1/2. Both landiolol and M1 were detected in urine, but only a small fraction (<10%) of the administered dose was excreted as intact parent compound in patients with hepatic impairment and healthy subjects (6.2% and 4.7%, respectively). The major component was identified as M1 (71.3% and 57.7% for patients with hepatic impairment and healthy subjects, respectively).

Clinical Trial of an Ultra Short Acting β1-Blocker; Landiolol Hydrochloride (ONO-1101), on Paroxysmal Atrial Fibrillation or Flutter and Paroxysmal Supraventricular Tachycardia-An Open Label, Dose Finding Study (Late Phase II Study)-

Publication: Kato et al., Rinsho Iyaku (Jpn. J. Clin. Pharmacol. Ther.), Vol. 13, Special Issue No. 19 (November), 4873 (53) – 4901 (81), 1997.

Study Objective: The study objective was to evaluate the efficacy, safety, and optimal dose of landiolol in the treatment of paroxysmal atrial fibrillation or flutter (PAF/PAFL) and paroxysmal supraventricular tachycardia (PSVT).

Reference ID: 5161679

Study Design: 123 patients (PAF/PAFL: 63, PSVT: 60) were enrolled, and landiolol was given at a dose of 0.063 mg/kg/min × 1 ml bolus infusion + 0.02 mg/kg/min × 10 min infusion in 41 patients (Group L), 0.125 mg/kg/min × 1 min bolus infusion + 0.04 mg/kg/min × 10 min infusion in 45 patients (Group M), and 0.25 mg/kg/min × 1 min bolus infusion + 0.08 mg/kg/min × 10 min infusion in 37 patients (Group H).

Efficacy assessment:

- Arrhythmia Improvement Rating

Based on the results throughout the period from start to end of administration, the change in arrhythmia was rated according to the following criteria.

(1) PAF/PAFL:

1: Substantial improvement (paroxysms terminated and normal sinus rhythm recovered or heart rate reduction by ≥30%)

2: Moderate improvement (paroxysms terminated intermittently or heart rate reduction by ≥20%)

3: Slight improvement (heart rate reduction by <20%)

4: No change (paroxysmal condition unchanged)

5: Worsened (marked increase in heart rate)

[6: Assessment impossible]

(2) PSVT:

1: Substantial improvement (paroxysms terminated and normal sinus rhythm recovered)

2: Moderate improvement (paroxysms terminated intermittently)

3: Slight improvement (heart rate lowered)

4: No change (paroxysmal condition unchanged)

5: Worsened (marked increase in heart rate)

[6: Assessment impossible]

- Improvement Rating in Subjective Symptoms

Based on the presence or absence of symptoms as well as changes in degree of severity, evaluation was performed using the following 7-point scale:

0: Absence of symptom(s) both prior to and after administration

1: Substantial improvement

2: Moderate improvement

3: Slight improvement

4: No change

5: Worsened

[6: Assessment impossible]

- Overall Improvement Rating

Improvement ratings in arrhythmia and in subjective symptoms were combined and assessment was carried out using the following 6-point scale:

1: Substantial improvement

2: Moderate improvement

3: Slight improvement

4: No change

5: Worsened

[6: Assessment impossible]

Efficacy Results:

PAF/PAFL: As shown Table 11, the ratio of cases in which the improvement in arrhythmia was rated “moderately improved” or better was: 55.6% in group L, 61.9% in group M and 69.2% in group H, i.e., no difference was observed among the 3 groups (C-A-trend test: p = 0.2198) with the highest rating being found in group H. Further, in group M, in 2 cases out of 21 (9.5%) paroxysms terminated and in 1/21 (4.8%) a paroxysm stopped intermittently; in group H, a paroxysm terminated in 1/13 (7.7%) and paroxysms stopped intermittently in 2/13 (15.4%) cases, respectively. In contrast, there was no case in which paroxysms terminated in group L.

Table 11. Improvement Rating in Arrhythmia (PAF/PAFL)

Admin. Group	Prom-nent	Mode-rate	Mild	No Change	Wor-sened	To-tal	Assess-ment im-possible	"moderate" or higher	C-A-Trend Test
L	3 (16.7)	7 (38.9)	6 (33.3)	2 (11.1)	0	18	1 (-)	10/18 (55.6)	N.S. p = 0.2198
M	5 (23.8)	8 (38.1)	3 (14.3)	5 (23.8)	0	21	0 (-)	13/21 (61.9)	
H	4 (30.8)	5 (38.5)	3 (23.1)	1 (7.7)	0	13	0 (-)	9/13 (69.2)	

( ): %, N.S.: not significant

Admin. Group	Cases in which paroxysm terminated	Cases in which Paroxysms stop-ped intermit-tently	Number of Cases
L	0	0	18
M	2 (9.5)	1 (4.8)	21
H	1 (7.7)	2 (15.4)	13

PSVT: As shown Table 12, the ratio of cases rated “moderately improved” or better was: 47.1% in group L, 57.1% in group M and 47.4% in group H (C-A-trend test: p = 0.5023). Further, as to cases in which paroxysms terminated and those in which paroxysms stopped intermittently: In

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group L, in 7/17 cases (41.2%) paroxysms terminated and in 1/21 (5.9%) it stopped intermittently; in group M, paroxysms terminated in 11/21 cases (52.4%) and in 1/21 (4.8%), a paroxysm stopped intermittently, while in group H, paroxysms terminated in 9/19 case (47.4%) and intermittent stopping of a paroxysm occured in 0/19 (0%). No difference was observed among the 3 groups.

Table 12. Improvement Rating in Arrhythmia (PSVT)

Admin. Group	Pro-minent	Mode-rate	Mild	No Change	Wors-ened	To-tal	Assess-ment im-possible	"moderate" or higher	C-A-Trend Test
L	8 (47.1)	0	6 (33.3)	3 (17.6)	0	17	0 (-)	8/17 (47.1)	N.S. p = 0.5023
M	11 (52.4)	1 (4.8)	6 (28.6)	3 (14.3)	0	21	0 (-)	12/21 (57.1)	
H	9 (47.4)	0	8 (42.1)	2 (10.5)	0	19	1 (-)	9/19 (47.4)	

( ): %, N.S.: not significant

Admin. Group	Cases in which paroxysm stopped	Cases in which which Paroxysm stopped inter-mittently	Cases in which Par-oxysms did not stop	To-tal
L	7 (41.2)	1 (5.9 %)	9 (52-9)	17
M	11 (52.4)	1 (4.8)	9 (42.9)	21
H	9 (47.4)	0	10 (52.6)	19

( ): %

Clinical Evaluation of An Ultra Short Acting β1-Blocker; Landiolol Hydrochloride (ONO-1101), on Perioperative Supraventricular Tachyarrhythmia –A Double-blind, Dose Finding Study (Late Phase II Study)–

Publication: Yoshiya et al., Rinsho Iyaku (Jpn. J. Clin. Pharmacol. Ther.), Vol. 16, No. 10, 1557(113) – 1577(133), 2000.

Study Objective: The study objective was to evaluate its efficacy, safety and optimal dose for landiolol in patients with perioperative supraventricular tachyarrhythmias.

Study Design: A total of 140 patients were enrolled, and landiolol was given at 3 doses; 0.031mg/kg/min × 1 min bolus infusion + 0.01 mg/kg/min × 10 min infusion in 49 patients

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(Group L), 0.063 mg/kg/min × 1 min bolus infusion + 0.02 mg/kg/min × 10 min infusion in 46 patients (Group M) and 0.125 mg/kg/min × 1 min bolus infusion + 0.04 mg/kg/min × 10 min infusion in 45 patients (Group H).

Efficacy assessment:

Depending on the type of tachycardia, the improvement in tachycardia was assessed as follows:

(a) Sinus tachycardia

Heart rate lowering during administration of the study medication until the end of the observation period 15 min after the end of administration was rated using the following five-point scale:

1: Substantial improvement (heart rate reduction ≥30%)

2: Moderate improvement (heart rate reduction ≥20%)

3: Slight improvement (heart rate reduction <20%)

4: No change (heart rate unchanged; variation <10%)

5: Worsening (heart rate increase ≥10%)

(b) Tachyarrhythmia

Changes in arrhythmia during administration of the study medication until the end of the observation period 15 min after the end of administration were rated using the following five-point scale:

1: Substantial improvement (paroxysm ceased and normal sinus rhythm was restored)

2: Moderate improvement (paroxysm ceased intermittently or heart rate reduction ≥20%).

3: Slight improvement (heart rate reduction <20%)

4: No change (state of paroxysm unchanged or heart rate unchanged; variation <10%)

5: Worsening (heart rate increase ≥10%)

Efficacy Results: The degree of improvement of tachyarrhythmia is shown in **Table 13**. The proportion of cases with improvement rated "moderate" or better was 67.4% in group L, 77.8% in group M and 90.7% in group H, with a significant dose correlation (C-A trend test: p = 0.0038).

Table 13. Improvement of Tachyarrhythmia

Admin Group	Substantial improvement	Moderate improvement	Slight improvement	No change	Worsened	Total	"Moderate improvement" or better (%)	C-A trend test
L	12	19	13	2	0	46	67.4	** p=0.0038
M	9	26	6	4	0	45	77.8	
H	19	20	4	0	0	43	90.7	

Reference ID: 5161679

4.3 References

Mitsuyoshi Nakashima and Mitsutaka Kanamaru, Phase I Study of ONO-1101, a New Ultra Short Acting β1-Blocking Agent in Healthy Volunteers. Rinsho Iyaku (Jpn. J. Clin. Therap. Med.), Vol. 16, Special Issue No. 10 (October), 1531(87) – 1556(112), 2000.

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Reference ID: 5161679

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Signing on behalf of myself and Snehal Samant (on extended leave).