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CLINICAL REVIEW(S)

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

CLINICAL REVIEW

Application Type	NDA
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Established/Proper Name	Landiolol hydrochloride
(Proposed) Trade Name	
Applicant	AOP Orphan Pharmaceuticals GmbH
Dosage Form(s)	Intravenous infusion
Applicant Proposed Dosing Regimen(s)	1. For patients with normal cardiac function, titrate using ventricular rate at 10-minute intervals: start at 10 mcg/kg/min; adjust dose as needed up to 40 mcg/kg/min in 10 mcg/kg/min increments to achieve desired reduction of ventricular rate. 2. For patients with impaired cardiac function titrate using ventricular rate at 15-minute intervals: Start at 1 mcg/kg/min, adjust dose as needed up to (b) (4) mcg/kg/min in 1 mcg/kg/min increments to achieve desired reduction of ventricular rate.
Applicant Proposed Indication(s)/Population(s)	A beta-1 adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.

Table of Contents

Glossary	10
1. Executive Summary.....	12
1.1. Product Introduction	12
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	12
1.3. Benefit-Risk Assessment.....	12
1.4. Patient Experience Data	20
2. Therapeutic Context	22
2.1. Analysis of Condition	22
2.2. Analysis of Current Treatment Options	23
3. Regulatory Background.....	31
3.1. U.S. Regulatory Actions and Marketing History.....	31
3.2. Summary of Presubmission/Submission Regulatory Activity.....	31
3.3. Foreign Regulatory Actions and Marketing History	32
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	32
4.1. Office of Scientific Investigations (OSI)	32
4.2. Product Quality.....	33
4.3. Clinical Microbiology	33
4.4. Nonclinical Pharmacology/Toxicology	33
4.5. Clinical Pharmacology.....	33
4.6. Devices and Companion Diagnostic Issues	34
4.7. Consumer Study Reviews.....	34
5. Sources of Clinical Data and Review Strategy	34
5.1. Table of Clinical Studies	34
5.2. Review Strategy	40
6. Review of Relevant Individual Trials Used to Support Efficacy.....	42
6.1. Kato et al. 1997.....	42
6.1.1. Study Design.....	42

6.1.2. Study Results	47
6.2. Yoshiya et al. 1997	58
6.2.1. Study Design	58
6.2.2. Study Results	61
6.3. Yoshiya et al. 2002	70
6.3.1. Study Design	70
6.3.2. Study Results	73
6.4. Tanaka et al. 2008.....	84
6.4.1. Study Design	84
6.4.2. Study Results	86
6.5. Taenaka and Kikawa 2013	90
6.5.1. Study Design	90
6.5.2. Study Results	93
6.6. Sakamoto et al. 2012	103
6.6.1. Study Design	103
6.6.2. Study Results	105
6.7. Nagai et al. 2013	110
6.7.1. Study Design	110
6.7.2. Study Results	113
6.8. Xiao et al, 2014	121
6.8.1. Study Design	121
6.8.2. Study Results	123
7. Integrated Review of Effectiveness.....	127
7.1. Assessment of Efficacy Across Trials	128
7.1.1. Primary Endpoints	129
7.1.2. Secondary and Other Endpoints.....	135
7.1.3. Subpopulations.....	135
7.1.4. Dose and Dose-Response	138
7.1.5. Onset, Duration, and Durability of Efficacy Effects.....	138
7.2. Additional Efficacy Considerations	139
7.2.1. Considerations on Benefit in the Postmarket Setting.....	139

7.2.2. Other Relevant Benefits	139
7.3. Integrated Assessment of Effectiveness	139
8. Review of Safety	141
8.1. Safety Review Approach	141
8.2. Review of the Safety Database	142
8.2.1. Overall Exposure	142
8.2.2. Relevant characteristics of the safety population:	146
8.2.3. Adequacy of the safety database:	146
8.3. Adequacy of Applicant’s Clinical Safety Assessments	147
8.3.1. Issues Regarding Data Integrity and Submission Quality	147
8.3.2. Categorization of Adverse Events	147
8.3.3. Routine Clinical Tests.....	149
8.4. Safety Results	150
8.4.1. Deaths	150
8.4.2. Serious Adverse Events (Hypotension)	150
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects	164
8.4.4. Significant Adverse Events.....	165
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions.....	171
8.4.6. Laboratory Findings	179
8.4.7. Vital Signs	179
8.4.8. Electrocardiograms (ECGs)	179
8.4.9. QT	183
8.4.10. Immunogenicity	183
8.5. Analysis of Submission-Specific Safety Issues	183
8.5.1. Hypotension	183
8.6. Safety Analyses by Demographic Subgroups	183
8.7. Specific Safety Studies/Clinical Trials	183
8.8. Additional Safety Explorations.....	183
8.8.1. Human Carcinogenicity or Tumor Development	183
8.8.2. Human Reproduction and Pregnancy.....	184
8.8.3. Pediatrics and Assessment of Effects on Growth	184

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	184
8.9. Safety in the Postmarket Setting	184
8.9.1. Safety Concerns Identified Through Postmarket Experience.....	184
8.9.2. Expectations on Safety in the Postmarket Setting.....	184
8.9.3. Additional Safety Issues From Other Disciplines.....	185
8.10. Integrated Assessment of Safety.....	185
9. Advisory Committee Meeting and Other External Consultations	186
10. Labeling Recommendations.....	186
10.1. Prescription Drug Labeling	186
10.2. Nonprescription Drug Labeling	187
11. Risk Evaluation and Mitigation Strategies (REMS)	187
12. Postmarketing Requirements and Commitments.....	188
13. Appendices	188
13.1. References	188
13.2. Financial Disclosure.....	190

Table of Tables

Table 1. Summary of Pharmacologic Treatments for Supraventricular Tachycardia (SVT).....	23
Table 2. Selected Clinical Trials Relevant to the Landiolol NDA.....	35
Table 3. Primary endpoint for each published clinical trial of landiolol.....	40
Table 4. Kato et al. 1997 Patient Disposition.....	47
Table 5. Reasons for patient exclusion from Kato et al. 1997	48
Table 6. Demographic characteristics of the primary effectiveness analysis from Kato et al. 1997	50
Table 7. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Kato et al. 1997	52
Table 8. Decrease in heart rate with landiolol treatment in Kato et al. 1997	52
Table 9. Subpopulation analysis of treatment effect in Kato et al. 1997.....	53
Table 10. Overall subjective patient improvement in Kato et al. 1997.....	56
Table 11. Changes in subjective symptoms in Kato et al. 1997	56
Table 12. Durability of heart rate response to landiolol in Kato et al. 1997	57
Table 13. Yoshiya et al. 1997 Patient Disposition.....	61
Table 14. Reasons for patient exclusion from Yoshiya et al. 1997.....	62
Table 15. Demographic characteristics of the primary effectiveness analysis from Yoshiya et al. 1997	65
Table 16. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Yoshiya et al. 1997	67
Table 17. Rate of switch to rescue treatment in Yoshiya et al. 1997.....	67
Table 18. Decrease in heart rate with landiolol treatment in Yoshiya et al. 1997	68
Table 19. Yoshiya et al. 2002 Patient Disposition.....	74
Table 20. Reasons for patient exclusion from Yoshiya et al. 2002.....	74
Table 21. Inclusion criteria met for Yoshiya et al. 2002.....	77
Table 22. Demographic characteristics from Yoshiya et al. 2002	78
Table 23. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Yoshiya et al. 2002	80
Table 24. Decrease in heart rate with landiolol treatment in Yoshiya et al. 2002.....	81
Table 25. Change in heart rate up to 5 minutes of administration in Yoshiya et al. 2002	82
Table 26. Heart rates 30 and 60 minutes after discontinuation in Yoshiya et al. 2002	84
Table 27. Tanaka et al. 2008 Patient Disposition.....	87
Table 28. Demographic characteristics from Tanaka et al. 2008.....	88
Table 29. Summary of landiolol effectiveness in the proposed post-hoc primary endpoint in Tanaka et al. 2008	89
Table 30. Taenaka and Kikawa 2013 Patient Disposition	93
Table 31. Reasons for patient exclusion from Taenaka and Kikawa 2013	94
Table 32. Demographic characteristics from Taenaka and Kikawa 2013.....	95
Table 33. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Taenaka and Kikawa 2013.....	98

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

Table 34. Decrease in heart rate with landiolol treatment in Taenaka and Kikawa 2013	99
Table 35. Subpopulation analysis of treatment effect in Taenaka and Kikawa 2013	102
Table 36. Patient disposition in Sakamoto et al. 2012.....	106
Table 37. Demographic characteristics from Sakamoto et al. 2012	107
Table 38. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Sakamoto et al. 2012	108
Table 39. Conversion to sinus rhythm in Sakamoto et al. 2012.....	109
Table 40. Nagai et al. 2013 Patient disposition	114
Table 41. Demographic characteristics from Nagai et al. 2013	115
Table 42. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Nagai et al. 2013	117
Table 43. Patient data at 48 hours of study drug administration in Nagai et al. 2013.....	120
Table 44. Xiao et al. 2014 Patient Disposition	123
Table 45. Demographic Characteristics from Xiao et al. 2014	125
Table 46. Baseline heart rate, blood pressure, electrocardiographics in Xiao et al. 2014	126
Table 47. Summary demographics for submitted randomized placebo-controlled trials.....	130
Table 48. Summary demographics for submitted active-controlled trials.....	130
Table 49. Summary of landiolol effectiveness on the post-hoc primary endpoint in placebo-controlled trials.....	133
Table 50. Summary of landiolol effectiveness on the post-hoc primary endpoint in active-controlled trials.....	134
Table 51. Common Baseline Attributes of the Clinical Trial Populations.....	135
Table 52. Safety Population, Size, and Denominators from Controlled Trials of Landiolol.....	143
Table 53. Description of Prevention-Only Placebo Controlled Studies of Landiolol	144
Table 54. Description of Prevention-Only Placebo Controlled Studies of Landiolol Continued.	145
Table 55. Published Placebo-Controlled Treatment and Prevention Population Adverse Events	148
Table 56. Frequency of Adverse Events from Landiolol Placebo-Controlled Clinical Trials.....	151
Table 57. Frequency of Adverse Events by Landiolol Dose in Treatment and Prevention Placebo-Controlled Trials.....	153
Table 58. Adverse Events of Special Interest in Treatment and Prevention Landiolol Clinical Trials	154
Table 59. Change in Blood Pressure or Presence of Hypotension in Placebo or Active Controlled Clinical Trials of Landiolol.....	155
Table 60. Adverse Events and Hypotension in Placebo-Controlled Clinical Treatment Trials of Landiolol	157
Table 61. Adverse Event Frequency for Placebo-Controlled Treatment Trials	167
Table 62. Adverse Event Frequency for Placebo-Controlled Treatment Trials Continued.....	168
Table 63. Adverse Event Frequency for Placebo-Controlled Treatment Trials Continued.....	169
Table 64. Serious and Non-Serious Adverse Events from Landiolol Post-Market Data	171
Table 65. Adverse events reported in Kato et al. 1997	172
Table 66. Adverse events reported in Yoshiya et al. 1997.....	173

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

Table 67. Adverse events reported in Yoshiya et al. 2002.....	175
Table 68. Adverse events reported in Taenaka and Kikawa 2013	176
Table 69. Adverse events reported in Sakamoto et al. 2012	177
Table 70. Adverse events reported in Nagai et al. 2013.....	178
Table 71. Adverse Events in Xiao et al. 2014	179
Table 72. Electrocardiograms reported in each landiolol clinical trial.....	180
Table 73. Changes in ECG parameters in response to landiolol in Kato et al. 1997.....	180
Table 74. Changes in ECG parameters with landiolol in Yoshiya et al. 1997.....	181
Table 75. Changes in ECG parameters in Yoshiya et al. 2002	182
Table 76. Changes in ECG parameters in Taenaka and Kikawa 2013.....	182

Table of Figures

Figure 1. Kato et al. 1997 Schedule of Events	44
Figure 2. Durability and persistence of heart rate response to landiolol in Kato et al. 1997.....	57
Figure 3. Yoshiya et al. 1997 Schedule of Events.....	59
Figure 4. Durability and persistence of heart rate response to landiolol in Yoshiya et al. 1997..	69
Figure 5. Yoshiya et al. 2002 Schedule of Events.....	71
Figure 6. Durability and persistence of heart rate response in Yoshiya et al. 2002.....	83
Figure 7. Durability and persistence of heart rate response in Taenaka and Kikawa 2013	101
Figure 8. Study schema for Nagai et al. 2013	112
Figure 9. Percentage of patients who achieved the primary endpoint by landiolol dose in Nagai et al 2013	118
Figure 10. Heart rate response to landiolol and digoxin in Nagai et al. 2013	119
Figure 11. Change in Heart Rate in Xiao et al. 2014	127
Figure 12. Blood pressure response to landiolol in Kato et al. 1997	158
Figure 13. Blood pressure response to landiolol in Yoshiya et al. 1997.....	159
Figure 14. Blood pressure response in Yoshiya et al. 2002	161
Figure 15. Blood pressure response in Taenaka and Kikawa 2013	162
Figure 16. Blood pressure following landiolol and digoxin administration in Nagai et al. 2013	163
Figure 17. Systolic blood pressure following landiolol administration in Xiao et al. 2014.....	164
Figure 18. Diastolic blood pressure following landiolol administration in Xiao et al. 2014	164

Glossary

AC	advisory committee
AE	adverse event
AF	atrial fibrillation
AFL	atrial flutter
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AT	atrial tachycardia
BLA	biologics license application
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BPM	beats per minute
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HR	heart rate
ICH	International Council for Harmonization
IND	Investigational New Drug Application

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association functional class
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PSVT	paroxysmal supraventricular tachycardia
REMS	risk evaluation and mitigation strategy
RCT	randomized controlled clinical trial
RPP	rate-pressure product
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SVT	supraventricular tachycardia
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Landiolol is an intravenous beta-1 adrenergic receptor antagonist with relatively short half-life intended to be administered at between 1 and 40 mcg/kg/min for the short-term reduction of ventricular rate in patients with supraventricular tachycardia (SVT), including atrial fibrillation and atrial flutter. Landiolol has regulatory approval for this indication in Europe (as Rapibloc) and Japan (as Onoact) but is a new molecular entity without regulatory approval in the United States. This application relies on the safety and effectiveness data exclusively from the published literature.

The sponsor proposes two dosing schemes based on the clinical context of the patient with supraventricular tachycardia to be treated: 1. Those with normal left ventricular myocardial contractile function, in whom the proposed starting dose is 10 mcg/kg/min for 10 min, followed by titration by 10 mcg/kg/min every 10 minutes to a maximum dose of 40 mcg/kg/min, and 2. Those with reduced left ventricular myocardial contractile function, in whom the proposed starting dose is 1 mcg/kg/min for 15 min, followed by titration by 1 mcg/kg/min every 15 minutes to a maximum dose of (b) (4) mcg/kg/min.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the data in the published literature from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials, landiolol hydrochloride was effective at decreasing heart rate (HR) for patients with supraventricular tachycardia (SVT), including atrial fibrillation (AF) and atrial flutter (AFL), and including for patients with a diagnosis of heart failure. Based on these same data landiolol hydrochloride caused a predictable, monitorable, and reversible decrease in blood pressure in the treated populations that could result in hypotension. These data support the safety and effectiveness of landiolol hydrochloride for the surrogate outcome of HR reduction in SVT. Therefore, the applicant has provided substantial evidence of effectiveness and safety of landiolol for the short-term reduction in ventricular rate in the intended population of patients with SVT including AF and AFL.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Based on the submitted randomized controlled clinical trial data from 8 published trials, intravenous infusion of landiolol hydrochloride appears to have a consistent and predictable treatment effect to lower heart rate (HR) in the short-term for hospitalized patients with supraventricular tachycardia (SVT) including atrial fibrillation (AF) and atrial flutter (AFL). SVT is a common condition in hospitalized patients with and without known cardiovascular disease, and it is generally presumed that HR lowering improves outcomes for patients with tachyarrhythmias within and outside of the perioperative setting. Landiolol appears to mediate the effect on HR by beta-adrenergic receptor antagonism, a well-understood mechanism of HR slowing. Although no individual-patient level data is available for patients treated with landiolol, placebo, or active controls utilized in the clinical trials to demonstrate safety and effectiveness of landiolol, because all the submitted clinical data comes from the published literature, the treatment effect size appears consistent and the adverse event rate predictable. The surrogate endpoint of short-term HR reduction in the hospitalized setting for the management of SVT was established as a clinically approvable endpoint during the Cardiovascular and Renal Drugs Advisory Committee in September of 1986. Varied dosing regimens were used in the published clinical trials, but the proposed starting dose of 10 mcg/kg/min for patients without heart failure, titrated according to HR response in 10 mcg/kg/min increments to a maximal dose of 40 mcg/kg/min, is reasonable in the context of the dosing regimens tested in clinical trials. However, there is no evidence of therapeutic benefit compared to other typically utilized and approved agents indicated for short-term HR slowing. Clinically relevant hypotension was the principal adverse event identified, which was clinically monitorable, and given the relatively rapid onset with initiation and resolution of the landiolol effect on HR and blood pressure (BP) with discontinuation, landiolol administration can be adjusted accordingly. A lower starting dose of 1 mcg/kg/min, titrated in 1 mcg/kg/min increments according to HR response to [REDACTED] (b) (4) mcg/kg/min, for patients with heart failure and reduced left ventricular ejection fraction appears sufficient for safe use in that population. As patients with hepatic impairment were not adequately studied, landiolol use should be avoided in patients with Child-Pugh Class B or C hepatic dysfunction. Otherwise, restricted use of landiolol to the hospitalized setting where continuous monitoring of HR and BP can be performed appears sufficient for its safe and effective use in the intended population of patients with SVT, including AF and AFL, for short-term control of HR. Overall, the available clinical trial data support regulatory approval of landiolol for time-limited use in a monitored hospitalized setting for select patients with tachycardia, as it has a similar benefit and risk profile as other approved agents for the same indication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Supraventricular tachycardia (SVT) occurs in approximately 2% of patients before surgery, and 6% of patients in the post-operative period, where the incidence of atrial arrhythmias peaks 2-3 days after surgery. Atrial fibrillation (AF) or flutter (AFL) occur in 20-50% of patients after cardiac surgery and 1-15% of patients after non-cardiac surgery. - It is presumed that lowering of heart rate (HR), blood pressure (BP), and the rate-pressure double product (HR x BP, or RPP), particularly for patients with coronary artery disease, will reduce myocardial ischemia and improve outcomes for patients with tachyarrhythmias within and outside of the perioperative setting. - In the September 29, 1986, Cardiovascular and Renal Drugs Advisory Committee in which the short-acting beta-1 adrenergic receptor antagonist esmolol was discussed, it was believed that the hypothesis that perioperative HR-slowing would decrease the rate of clinical outcomes was untestable due to the universal application of this hypothesis in routine current clinical practice. However, it was also believed that HR lowering should be an accepted surrogate endpoint for effectiveness in the acute inpatient monitored tachycardic setting, noting that the theoretical benefit of HR slowing must be weighed against the risks of hypotension, bradycardia, and reduction in ventricular contractility.	SVT is a common clinical event in hospitalized patients with and without cardiovascular risk factors or known disease in the perioperative and non-perioperative setting. Based on the September 29, 1986, Cardiovascular and Renal Drugs Advisory Committee meeting, HR lowering for hospitalized patients with SVT including AF and AFL is a recognized surrogate endpoint for benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- Currently approved and available intravenous medications for the short-term control of tachycardia include the beta-adrenergic receptor antagonists esmolol and propranolol, the calcium channel antagonists diltiazem and verapamil, as well as the agents digoxin and adenosine, all of which are used to manage tachyarrhythmias in current clinical practice. Off-label intravenous metoprolol tartrate and amiodarone are also used in clinical practice. - The short-acting beta-adrenergic antagonist esmolol is most pharmacokinetically similar to landiolol. Esmolol was approved based on 2 multicenter randomized controlled double-blinded multicenter parallel group clinical trials, wherein esmolol was compared with placebo and propranolol. Each trial used identical patient selection criteria, esmolol treatment schedule, and prespecified endpoint. Esmolol was titrated from 50 to 500 mcg/kg/min at 4-minute intervals and when therapeutic response was achieved the patient was treated for 30-240 additional minutes at that dose. All patients were hospitalized with SVT and HR >120 beats per minute (bpm) lasting for ≥30 minutes. Patients with BP <100/70 mmHg or New York Heart Association functional class (NYHA) III and IV heart failure were excluded. - In the esmolol trials of patients with SVT and primarily AF or AFL, the primary effectiveness endpoint was a composite of either a ≥20% decrease in HR from baseline, decrease in HR to <100 bpm, or conversion to sinus rhythm with treatment.	The short-acting beta-1 adrenergic receptor antagonist esmolol is currently available and clinically used for the short-term management of SVT including AF and AFL. The non-selective beta-adrenergic antagonist propranolol may also be used in this situation, as can the intravenous non-dihydropyridine calcium channel blockers diltiazem or verapamil, or digoxin. The elimination half-lives for propranolol and diltiazem are on the order of multiple hours, and the other agents longer, whereas the elimination half-life for esmolol is approximately 9 minutes. Esmolol is therefore the most directly comparable drug for the indication proposed for landiolol. Esmolol was evaluated in the September 29, 1986, Cardiovascular and Renal Drugs Advisory Committee meeting for a comparable indication as that proposed for landiolol; esmolol was approved based on 2 multicenter RCTs compared with placebo and propranolol for the primary effectiveness endpoint of HR reduction. The primary adverse event was hypotension. The agency approved esmolol for the indication of heart rate control, it is “indicated for the short-term treatment of: control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory sinus tachycardia; control

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The primary safety event with esmolol was hypotension, defined as a BP <90/50 mmHg, which occurred in 25% of treated patients, 12% of which were symptomatic. In 80% of patients with hypotension, hypotension resolved within 30 minutes of esmolol discontinuation.	of perioperative tachycardia and hypertension.” Therefore, there exist multiple approved safe and effective treatment options for the targeted patient population and clinical condition.
Benefit	- Landiolol was administered by intravenous infusion at rates between 1 and 80 mcg/kg/min in the published clinical trials and titrated to the clinical effect on HR reduction. - A statistically and clinically significantly greater proportion of patients with SVT and tachycardia treated with landiolol had decreased HR compared to placebo, according to the proposed post-hoc primary composite endpoint of either a ≥20% decrease in HR from baseline, decrease in HR to <100 bpm, or conversion to sinus rhythm with treatment. The treatment effects were generally large and their assessment does not rely on complicated statistical methodologies nor formal meta-analysis. - Compared to placebo, between 42% and 89% of patients treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 0-11% of patients did if treated with placebo. Within each of the submitted clinical trials, the statistical hypothesis test for each supported a difference in treatment effect between landiolol and placebo. - Compared to active control, 43% of patients with heart failure treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 12% did with digoxin treatment.	From the data submitted from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials, landiolol was effective at decreasing HR for patients with SVT, specifically AF and AFL, and including patients with a diagnosis of heart failure. Although the primary endpoint is post-hoc, the primary endpoint was often a component of the primary endpoint from the original published clinical trials, and the effect size appears large for the surrogate endpoint defined and previously approved for esmolol. Although the clinical trials were performed exclusively outside of the US, principally in Japan and China, the data are clinically applicable to patients in the US, and it is expected that patients in the US will respond similarly to this specific beta-adrenergic receptor antagonist as they do to other similar agents that have evidence for effectiveness in the US population. Although there is no evidence of biased publication, specifically clinical trials with landiolol

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The submitted clinical trial publications utilized heterogeneous populations with non-uniform inclusion and exclusion criteria, variable dosing and titration regimens, and distinct primary endpoints, and the primary endpoint was post-hoc. However, the overall effectiveness of landiolol treatment on HR for patients with SVT was consistent among the submitted clinical trials. - The treatment effect for landiolol was consistent for patients with tachycardia and heart failure with a reduced left ventricular ejection fraction. - There was no evidence for a dose-response relationship between landiolol and the proportion of patients who experienced a reduction in HR in the clinical trials. The proposal to label the lower range of tested doses, specifically intravenous infusions of 10 to 40 mcg/kg/min for patients without heart failure, and 1 to (b)(4) mcg/kg/min for patients with heart failure, is concordant with the available data for effectiveness. - The treatment effect of landiolol appears durable and consistent during continuous infusion from 5 minutes up to 24 hours and appears to persist for approximately 30 minutes after infusion discontinuation in the majority of patients.	that may have been performed but did not show evidence of a treatment effect on HR that may have been excluded from publication, and although such publication bias cannot be conclusively ruled out, the evidence of a treatment effect for landiolol in the enrolled populations is consistent among the multiple clinical trials performed by multiple investigators at multiple distinct institutions, all unconnected with the current applicant over multiple time periods. Thus, the potential for systematic publication bias that would substantially contradict the published evidence is considered low. Therefore, the applicant has provided substantial evidence of effectiveness of landiolol for the short-term reduction of HR in the intended population of patients with SVT.
Risk and Risk Management	- No individual patient safety data was submitted as part of the application. Safety assessment was only possible from the published captured adverse events (AE), with the potential for missed ascertainment and no avenue to interrogate the primary medical records, ascertainment protocols, or investigators for the submitted clinical trials. - The safety database contained 568 landiolol-treated	Based on the data submitted from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials, landiolol causes a predictable, monitorable, and reversible decrease in blood pressure in the treated populations with associated events of clinical hypotension. The adverse event of hypotension is both clinically monitorable and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients enrolled in randomized controlled clinical trials for the treatment of SVT, and safety data were available for 962 patients treated with landiolol in placebo-controlled trials of either SVT treatment or prevention. • The landiolol-associated AE of greatest incidence and seriousness was hypotension. The risk of hypotension varied by the clinical trial population, but no specific predictors of increased risk of hypotension were identified. Although the inclusion criteria with regards to enrollment BP and HR were not consistently defined, hypotension was clinically monitorable and typically reversible, generally over the course of 30 minutes, with landiolol discontinuation. • Although the rate of reported adverse events from large numbers of submitted observational studies was lower, hypotension occurred in 44 of 445 patients included in the randomized placebo-controlled treatment trials, giving a rate of 9.9%, compared to 5 of the 395 patients who received placebo, with a rate of 1.3%. • The rate of landiolol discontinuation due to AE was 2.3%, occurring in 13 of 568 patients in the randomized controlled clinical trials with adequate safety reporting, including those patients with heart failure. • There was no evidence of association of clinical trial infusion dose with the rate of AEs or hypotension. However, the dose of landiolol utilized in the clinical trial for patients with known heart failure was lower than for those patients	typically reversible with landiolol removal. General regulatory understanding of the mechanism of action through beta-adrenergic receptor antagonism and the use of similar medications for this patient population add to the regulatory comfort with this agent. Therefore, the applicant has provided evidence of safety of landiolol for the intended use in the population of patients with SVT including patients with AF and AFL. As patients with hepatic impairment have not been adequately studied, landiolol use should be avoided in patients with Child-Pugh Class B or C hepatic dysfunction. No additional risk management strategies are required beyond the recommended labeling with expected continuous monitoring of HR and BP in the hospitalized setting, as well as use of lower dose with slower titration of landiolol for patients with heart failure.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	without heart failure, and the dose was titrated to a lower maximal dose and increased at a slower rate. • There is insufficient data regarding use of landiolol and appropriate dosing for patients with hepatic impairment, specifically Child-Pugh Class B or C disease.	

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

1.4. **Patient Experience Data**

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Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

No patient experience data was submitted.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

☐	Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Non-sinus rhythm SVTs by definition are tachycardias with HR>100 bpm of supraventricular origin, contrasted with ventricular tachycardias, and they occur in the perioperative and non-perioperative settings. The most common is atrial fibrillation (AF), then atrioventricular nodal reentrant tachycardia (AVNRT), then atrial flutter (AFL) and atrioventricular reentrant tachycardia (AVRT). Prevalence of SVT in the general population is 2.25 cases/1000 persons and incidence is 35 cases/100,000 person-years, with women at twice the risk of men.¹

SVT may be associated with symptoms including palpitations, lightheadedness, fatigue, malaise, chest pain, dyspnea, presyncope, and syncope, and may be associated with clinical instability and hypotension in the acute care, intensive care, and perioperative settings. Symptoms and the clinical impact of SVT may be worse in patients with cardiovascular comorbidities including obstructive coronary atherosclerosis.

Diagnosis is typically made by surface electrocardiography, particularly in the inpatient hospital or emergency department setting where the intravenous agent landiolol would be used.

¹ Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, Calkins H, Corrado D, Deftereos SG, Diller GP, Gomez-Doblas JJ, Gorenek B, Grace A, Ho SY, Kaski JC, Kuck KH, Lambiase PD, Sacher F, Sarquella-Brugada G, Suwalski P, Zaza A; ESC Scientific Document Group. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020 Feb 1;41(5):655-720.

Clinical Review
 Mitchell Psofka, MD PhD
 NDA 217202
 Landiolol hydrochloride

During the Cardiovascular and Renal Drugs Advisory Committee meeting on September 29, 1986, the need for a beta-blocking agent for use in critical care settings was discussed.² For patients in whom an SVT is transient “control of ventricular rate with an easily titrated drug is clinically indicated.”

2.2. Analysis of Current Treatment Options

Multiple drugs are approved for the acute management of SVT in the acute setting, and additional unapproved medications are also utilized. Nonpharmacologic interventions included direct-current cardioversion for acutely hemodynamically unstable or hypotensive patients, hemodynamically stable patients who are awake may be asked to perform vagal maneuvers or in some cases have carotid sinus massage performed. If these nonpharmacologic interventions are not indicated or not possible, then approved pharmacologic therapies are used including beta-1 selective and non-selective beta-adrenergic antagonists and non-dihydropyridine calcium channel blockers. Other non-approved agents are also used in common practice including metoprolol tartrate, amiodarone, and digoxin. The agent with the closest indication to that proposed for landiolol is esmolol, listed first in Table 1.

Table 1. Summary of Pharmacologic Treatments for Supraventricular Tachycardia (SVT)

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Esmolol (Brevibloc) ³	A beta-adrenergic blocker indicated for the short-term treatment of: Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter and control of heart rate in noncompensatory	1986	Intravenous, continuous infusion; optional loading dose; treatment up to 48 hours.	Two RCT of patients with SVT comparing esmolol to propranolol or placebo for a ≥20% decrease in HR from baseline, decrease in HR	In the two RCTs, hypotension (BP <90/50 mmHg) occurred in 27 of 50 patients with esmolol (54%), 4 (8%) symptomatic, and 10 of 55 patients with propranolol

² https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/19-386_Brevibloc_AdminCorres.pdf

³ https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019386s043lbl.pdf

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	sinus tachycardia; Control of perioperative tachycardia and hypertension.			to <100 bpm, or conversion to sinus rhythm. Therapeutic success in 36 of 50 patients with esmolol (72%) and 38 of 55 patients with propranolol (69%). Therapeutic success in 39 of 61 patients with esmolol (64%) and 3 of 39 patients with placebo (8%).	(18%), hypotension occurred without relationship to esmolol dose. Hypotension (BP <90/50 mmHg) occurred in 16 of 61 patients with esmolol (26%), 7 symptomatic, and 1 of 39 patients with placebo (3%). Hypotension occurred across the dosing range. In 80% of patients, hypotension resolved 30 minutes after esmolol discontinuation.
Adenosine (Adenocard) ⁴	Conversion to sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including that associated with accessory bypass tracts (Wolff-Parkinson-White Syndrome). When	1989	Intravenous rapid bolus; up to 3 repeated intravenous boluses may be given.	Adenocard does not convert atrial flutter, atrial fibrillation, or ventricular tachycardia to normal sinus rhythm. In the presence of	Contraindicated in: 1. Second- or third-degree A-V block (except in patients with a functioning artificial pacemaker). 2. Sinus node

⁴ https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019937s024lbl.pdf

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	clinically advisable, appropriate vagal maneuvers (e.g., Valsalva maneuver), should be attempted prior to Adenocard administration.			atrial flutter or atrial fibrillation, a transient modest slowing of ventricular response may occur immediately following Adenocard administration.	disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker). 3. Known hypersensitivity to adenosine.
Diltiazem (Cardizem) ⁵	A non-dihydropyridine calcium-channel blocker indicated for the following: Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.	1982	Intravenous bolus or infusion	In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of diltiazem hydrochloride injection was effective in reducing heart rate by at least 20% in 95% of patients.	Hypotension was the most commonly reported adverse event during clinical trials, with symptomatic hypotension occurring in 3.2% of patients Diltiazem is a negative inotrope and can cause decreased systolic function and heart failure. The plasma elimination half-

⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215252s000lbl.pdf

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

					life is approximately 3.4 h.
Propranolol hydrochloride ⁶	A nonselective beta-adrenergic receptor blocker, Intravenous administration is usually reserved for life-threatening arrhythmias or those occurring under anesthesia. Intravenous propranolol is indicated for the short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate. Use in patients with atrial flutter or atrial fibrillation should be reserved for arrhythmias unresponsive to standard therapy or when more prolonged control is required. Intravenous propranolol is indicated to abolish tachyarrhythmias due to	1967	Intravenous bolus	In a series of 225 patients with supraventricular (n=145), ventricular (n=69), or both (n=11) arrhythmias resistant to digitalis, intravenous propranolol hydrochloride was administered in single doses, averaging 1 to 5 mg. Approximately one-quarter of the patients with supraventricular arrhythmias (generally those with sinus or atrial tachycardia) reverted to normal	The elimination half-life (T_{1/2} beta) is between 2 and 5.5 hours. Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; and 4) in patients with known hypersensitivity to propranolol hydrochloride.

⁶ https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/016419s029lbl.pdf

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	excessive catecholamine action during anesthesia when other measures fail.			sinus rhythm. About one-half had symptoms ameliorated either by a decrease in ventricular rate or an attenuation of frequency or severity of paroxysmal attacks.	
Verapamil (Calan) ⁷	A non-dihydropyridine calcium-channel blocker indicated for the treatment of supraventricular tachyarrhythmias, including: Rapid conversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory bypass tracts (Wolff-Parkinson-White [WPW] and Lown-Ganong-Levine [LGL] syndromes). When clinically advisable, appropriate vagal	1984	Intravenous bolus and infusion	In controlled studies in the U.S., about 60% of patients with supraventricular tachycardia converted to normal sinus rhythm within 10 minutes after intravenous verapamil HCl. Uncontrolled studies reported in the world literature describe a conversion rate of about 80%. About 70% of	Verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life about 4 minutes) and a slower terminal elimination phase (half-life 2-5 hours). The effect of a single injection lasts for 30–60 minutes when conversion to sinus rhythm does not occur. Intravenous

⁷ https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019038s004lbl.pdf

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	maneuvers (e.g., Valsalva maneuver) should be attempted prior to CALAN administration. Temporary control of rapid ventricular rate in atrial flutter or atrial fibrillation, except when the atrial flutter and/or atrial fibrillation are associated with accessory bypass tracts (Wolff-Parkinson-White [WPW] and Lown-Ganong-Levine [LGL] syndromes).			patients with atrial flutter and/or fibrillation with a fast ventricular rate respond with a decrease in heart rate of at least 20%.	verapamil often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness. Systolic pressure less than 90 mm Hg and/or diastolic pressure less than 60 mm Hg was seen in 5%-10% of patients in controlled U.S. trials in supraventricular tachycardia and in about 10% of the patients with atrial flutter/fibrillation.
Other Treatments ⁸					
Metoprolol tartrate	A beta1-selective beta-adrenergic receptor inhibitor indicated for	1984	Intravenous bolus doses at 2-minute		Plasma half-life ranges from approximately 3

⁸ Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, Calkins H, Corrado D, Deftereos SG, Diller GP, Gomez-Doblas JJ, Gorenek B, Grace A, Ho SY, Kaski JC, Kuck KH, Lambiase PD, Sacher F, Sarquella-Brugada G, Suwalski P, Zaza A; ESC Scientific Document Group. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2020 Feb 1;41(5):655-720. doi: 10.1093/eurheartj/ehz467. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4258. PMID: 31504425.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

(Lopressor) ⁹	the treatment of definite or suspected acute myocardial infarction in hemodynamically stable patients to reduce cardiovascular mortality when used in conjunction with oral metoprolol maintenance therapy.		intervals		to 7 hours. Most common adverse reactions: tiredness, dizziness, shortness of breath, bradycardia, hypotension, pruritus. Worsening cardiac failure may occur during metoprolol use.
Amiodarone (Codarone) ¹⁰	A class III anti-arrhythmic indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.	1995	Intravenous bolus and infusion		Hypotension is the most common adverse effect. In clinical trials, treatment emergent, drug-related, hypotension was reported as an adverse effect in 288 (16%) of 1836 patients treated with Codarone IV.
Digoxin (Lanoxin) ¹¹	A cardiac glycoside indicated for: Treatment of mild to moderate	1954	(b) (4)	In 3 randomized, double-blind trials that	The overall incidence of adverse reactions

⁹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/018704s027,028lbl.pdf

¹⁰ https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20377S002_CORDARONE_PRNTLBL.PDF

¹¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/009330Orig1s036lbl.pdf

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	heart failure in adults; Increasing myocardial contractility in pediatric patients with heart failure; Control of resting ventricular rate in adults with chronic atrial fibrillation.			included a total of 315 adult patients, digoxin was compared to placebo for the conversion of recent-onset atrial fibrillation to sinus rhythm. Conversion was equally likely, and equally rapid, in the digoxin and placebo groups. In a randomized 120-patient trial comparing digoxin, sotalol, and amiodarone, patients randomized to digoxin had the lowest incidence of conversion to sinus rhythm, and the least satisfactory rate control when conversion did not occur.	with digoxin has been reported as 5-20%, with 15-20% of adverse events considered serious. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse events.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Landiolol is a new molecular entity (NME) and not currently approved or marketed in the United States under consideration for the indication of the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.

3.2. Summary of Presubmission/Submission Regulatory Activity

- Initial Type B Meeting on September 6, 2016:

AOP, the applicant, expressed plans to seek approval based on nonclinical and clinical evidence from the published literature and nonclinical data from applicant-performed studies as part of a section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act application. A 505(b)(2) application is a new drug application (NDA) “for which one or more of the investigations relied upon by the applicant for approval ‘were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.’”¹² Concerns were expressed by the FDA Division regarding the sparse reporting of adverse events in the published literature. The sponsor indicated that they do not have access to any data (protocols, CSRs, SAPs) from the Japanese clinical trials. The evidence to support safety will come from adverse events observed for landiolol and comparators in controlled Japanese studies as published in the literature. The reported safety database included over 900 participants exposed to landiolol as reported by the applicant, which was believed may be sufficient from the Division. The applicant also provided in vitro study data on landiolol effects on cardiac ion channels.

- Type C Meeting February 16, 2017:

AOP proposed plans for manufacture of the Landiolol hydrochloride drug substance. Clinical issues were not discussed.

¹² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2>

Clinical Review
Mitchell Psozka, MD PhD
NDA 217202
Landiolol hydrochloride

- Type C Written Response Only June 30, 2017:

[Redacted content] (b) (4)

- Type C Meeting on July 14, 2020:

It was agreed that the primary clinical support for the planned marketing application for landiolol was to be provided by the published clinical literature. A meta-analysis of the published data for effectiveness of landiolol was proposed but discarded due to extensive trial heterogeneity regarding design, dosing, and patient selection.

- Type B Pre-NDA Meeting January 25, 2022:

The Division of Cardiology and Nephrology and the applicant agreed upon a post-hoc primary effectiveness endpoint for landiolol hydrochloride therapy to facilitate comparison of treatment effectiveness across published studies in patients with SVT. This endpoint is the responder analysis composite of:

- A decrease in HR $\geq$ 20%, or
- Achievement of HR $\leq$ 100 bpm, or
- Terminated paroxysm of SVT.

3.3. Foreign Regulatory Actions and Marketing History

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride
No OSI audit was requested.

4.2. **Product Quality**

Based on the most recent OPQ and CMC update, the drug product manufacturing facility, Lyocontract GmbH, is not approvable. A previous pre-approval inspection for another lyophilized product was unacceptable. The observations concerned cross-contamination of non-potent drug products with potent products and aseptic processing. A report from the applicant that the contamination has been addressed is needed and a follow-up inspection is needed to verify the corrective actions.

4.3. **Clinical Microbiology**

No clinically relevant clinical microbiology concerns have been identified.

4.4. **Nonclinical Pharmacology/Toxicology**

No clinically relevant clinical nonclinical pharmacology concerns have been identified.

4.5. **Clinical Pharmacology**

Landiolol is an injectable beta-1-adrenergic antagonist. It is supplied as a lyophilized powder in 50 mL single-dose vial equivalent to 300 mg of landiolol hydrochloride or 280 mg landiolol base.

The clinical data for landiolol primarily comes from studies performed outside of the United States and principally in a Japanese population. While no direct pharmacokinetic comparison was performed between Japanese patients and the more heterogenous United States patient population, the applicant did perform clinical pharmacokinetic studies in participants in the United States while the published pharmacokinetic data was performed in Japanese patients. From comparison of these pharmacokinetic studies, it appears that exposure of landiolol is higher in Japanese healthy adults compared to that in non-Japanese healthy adults, but there is little data on direct comparison.

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

Renal excretion of landiolol accounts for 4.3-9.2% of total clearance of landiolol. The mean terminal elimination half-life is approximately 3.2-4.5 minutes. There remains incomplete understanding of the potential impact of hepatic impairment on the clearance of landiolol.

The applicant did not conduct a clinical pharmacokinetics study in participants with impaired hepatic function, but the geometric mean C_{max} and AUC were increased by 42% and 44% in patients with hepatic impairment (5 patients with Child-Pugh class A and one patient with Child-Pugh class B) in Takahata et al. 2005.¹³

There remains incomplete understanding of the potential impact of drug-drug interaction (DDI) effects on the clearance of landiolol. The applicant did not conduct any in vitro or in vivo DDI assessments. However, neither landiolol nor its metabolites M1 and M2 demonstrate inhibitory effects on CYP1A2, 2C9, 2C19, 2D6, and 3A4 based on in vitro assessment.

4.6. Devices and Companion Diagnostic Issues

The application does not include a companion device or diagnostic.

4.7. Consumer Study Reviews

No label comprehension, patient self-selection, or other human factor studies were submitted for evaluation.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

¹³ Takahata T, Yasui-Furukori N, Sakamoto J, Suto K, Suto T, Tateishi T, Munakata A. Influence of hepatic impairment on the pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra-short-acting beta1-blocker. *Drugs R D*. 2005;6(6):385-94.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 2. Selected Clinical Trials Relevant to the Landiolol NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
Kato (1997)		Randomized double-blinded placebo-controlled clinical trial	Landiolol bolus 250 mcg/kg then 80 mcg/kg/min for 10 minutes	Primary: decrease in HR at 11 minutes	11 minutes	108	hospitalized patients with nonsurgical atrial fibrillation, HR>100 bpm, BP>100/70 mmHg	57 centers in Japan
Yoshiya (1997)		Randomized double-blinded placebo-controlled clinical trial	Landiolol bolus 125 mcg/kg then 40 mcg/kg/min for 10 min	Primary: decrease in HR at 5 minutes	11 minutes	284	patients with ischemia or hypertension with perioperative SVT during anesthesia, HR≥100	46 centers in Japan
Yoshiya (2002)		Randomized double-blinded placebo-controlled clinical trial	Landiolol bolus 125 mcg/kg then 40 mcg/kg/min for 10 min	Primary: decrease in HR at 11 minutes	11 minutes	58	patients with ischemia or hypertension with perioperative SVT, HR≥120 or HR≥100 & RPP≥15000 or ECG changes	19 centers in Japan
Tanaka (2008)		Randomized trial	Landiolol as a titrated bolus	Primary: proportion with	22 minutes	12	patients with ischemia & post-	1 center in Japan

Clinical Review
 Mitchell Psofka, MD PhD
 NDA 217202
 Landiolol hydrochloride

			between 30-125 mcg/kg then 10-40 mcg/kg/min for 10 min	decrease HR $\geq$ 20% & HR<100 bpm at 11 or 22 mi			operative SVT, HR $\geq$ 120 & ECG changes	
Taenaka & Kikawa (2013)		Randomized double-blinded placebo-controlled clinical trial	Landiolol as a titrated bolus between 30-125 mcg/kg then 10-40 mcg/kg/min for 10 min	Primary: proportion with decrease HR $\geq$ 20% & HR<100 bpm at 11 or 22 min	22 minutes	165	patients with ischemia or hypertension & post-operative SVT & ECG changes with HR $\geq$ 120 bpm	38 centers in Japan
Sakamoto (2012)		Randomized double-blinded active-controlled clinical trial, compared to diltiazem	Landiolol with no bolus, titrated 0.5-40 mcg/kg/min for 24 hours; diltiazem 0.25 mg/kg bolus then 3-15 mg/h	Primary: proportion converted to sinus rhythm at 8 hours	24 hours	71	patients with post-cardiac surgery atrial fibrillation/flutter, HR $\geq$ 100, LVEF $\geq$ 35%, BP $\geq$ 90/60	36 centers in Japan
Nagai (2013)		Randomized double-blinded active-controlled clinical trial, compared to digoxin	Landiolol with no bolus, titrated 1-10 mcg/kg/min for 2-48 hours; digoxin 0.25 mg intravenous bolus	Primary: proportion with decrease HR $\geq$ 20% & HR<110 bpm at 2 hours	2-48 hours	214	patients with heart failure NYHA III-IV & nonsurgical atrial fibrillation/flutter, HR $\geq$ 100, LVEF $\geq$ 20-50%, SBP $\geq$ 90; mean LVEF 36.6%	95 centers in Japan
Xiao (2014)	ChiCTRTRC-12003021	Randomized double-blinded placebo-	Landiolol bolus 125 mcg/kg then 40 mcg/kg/min for 10 min	Primary: proportion who received esmolol rescue when	5-60 minutes	240	Patients with intraoperative SVT with HR $\geq$ 100, or lasting >1	8 centers in China

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

		controlled clinical trial		decrease HR≤10% at 5 min			minute, or sinus HR≥100 for 3 minutes	
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
CPA368-10		double-blind crossover study to individuals concomitantly receiving an infusion of dobutamine	landiolol infusion at 10 mcg/kg/min and esmolol at 50 mcg/kg/min	Pharmacokinetics & time to reach a HR decrease of 10 bpm, 20 bpm, and the maximum HR effect	60-minute infusion	16	healthy participants	single center
CPA410-12		double blind crossover study with 3 healthy individuals in the pilot phase and 12 healthy individuals in the comparison phase	landiolol boluses at 100, 200, and 300 mcg/kg, landiolol boluses at 100, 200, and 300 mcg/kg, and esmolol boluses at 500, 1000, and 1500 mcg/kg, compared to placebo	Pharmacokinetics & BP, HR, ECG parameters	bolus dosing	15	healthy participants	single center
CPA422-12		double blind randomized crossover	landiolol lyophilizate infusions at 10 mcg/kg/min for 2 hours, then 20 mcg/kg/min for 2 hours, then 40 mcg/kg/min for 20	Pharmacokinetics & BP, HR, ECG parameters	24-hour infusion	14	healthy participants	single center

Clinical Review
 Mitchell Psozka, MD PhD
 NDA 217202
 Landiolol hydrochloride

			hours; compared to esmolol infusions at 50 mcg/kg/min for 2 hours, then 100 mcg/kg/min for 2 hours, then 200 mcg/kg/min for 20 hours					
LDLL600.201		open-label randomized study of landiolol targeting a heart rate <90 bpm or at least 20% reduction from baseline, which if not achieved the dose was increased to 80 mcg/kg/min after 16 minutes. After 180 minutes of therapy, a transition to	landiolol as either a bolus of 100 mcg/kg/min for 1 minute then as an infusion of 40 mcg/kg/min for up to 211 minutes; or, a continuous infusion at 40 mcg/kg/min without bolus for up to 210 minutes	Pharmacokinetics & achieving HR < 90 bpm or ≥ 20% reduction of HR from baseline	up to 211-minute infusions	20	10 adult patients with atrial fibrillation or atrial flutter and ventricular rates 100-200 bpm with clinical symptoms treated with each regimen	single center

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

		oral therapy was initiated.						

5.2. Review Strategy

The applicant submitted landiolol hydrochloride for the control of HR in the setting of SVT including AF and AFL. In the September 29, 1986 Cardiovascular and Renal Drugs Advisory Committee in which the short-acting beta-1 adrenergic receptor antagonist esmolol was discussed, it was believed that the hypothesis that perioperative HR-slowing would decrease the rate of clinical outcomes was untestable due to the universal application of this hypothesis in routine current clinical practice.¹⁴ Esmolol was given full approval and the label indication “for short-term treatment of: Control of ventricular rate in supraventricular tachycardia including atrial fibrillation and atrial flutter.”¹⁵ Therefore, HR lowering was judged to be an accepted pharmacodynamic surrogate endpoint for effectiveness in the setting of elevated heart rate due to supraventricular tachycardia including AF and AFL.

However, in this 505(b)(2) application, all of the clinical data comes from the published literature without any submitted individual patient data. Because the submitted clinical trials used disparate clinical populations, landiolol doses, durations, and primary endpoints, with variable collection of safety data, collective interpretation of each of the clinical trials’ data is needed to understand the clinical safety and effectiveness of landiolol. In order to summarize the data on landiolol clinical effectiveness, the sponsor proposed that the submitted randomized controlled clinical trial data was analyzed with respect to the primary post-hoc proposed endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. While this is a reasonable summary composite with which to compare the data between the trials, the trials were each judged on their own merits with regards to their stated primary endpoints (as described in Table 3), analysis methods, and data acquisition.

Table 3. Primary endpoint for each published clinical trial of landiolol

Study Citation	Primary Efficacy Endpoint per Publication
Kato et al. 1997	Moderate improvement of heart rate defined as paroxysm terminated intermittently or heart rate reduction $\geq 20\%$ from baseline at 11 minutes
Yoshiya et al. 1997	- Proportion of patients switched to rescue treatment if the heart rate reduction was $< 10\%$ after 7 minutes of treatment at - Secondary endpoint was moderate improvement of heart rate defined as a heart rate reduction $\geq 20\%$ from baseline

¹⁴ https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/19-386_Brevibloc_AdminCorres.pdf

¹⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205703s000lbl.pdf

Yoshiya et al. 2002	Moderate improvement of heart rate defined as a heart rate reduction $\geq 20\%$ from baseline at 11 minutes
Tanaka et al. 2008	Although the primary endpoint is not explicitly stated, it appears to be the proportion of patients who achieve a heart rate reduction of $\geq 20\%$ from baseline as well as a heart rate < 100 bpm at 11 or 22 minutes
Taenaka and Kikawa 2013	Moderate improvement of heart rate defined as a heart rate reduction $\geq 20\%$ from the baseline and a heart rate of < 100 bpm at 11 or 22 minutes
Sakamoto et al. 2012	- Proportion of patients that converted to sinus rhythm from atrial fibrillation after 8 hours - Secondary endpoint was reduction in heart rate to < 90 bpm
Nagai et al. 2013	Heart rate reduction $\geq 20\%$ from baseline as well as heart rate < 110 bpm at 2 hours
Xiao et al. 2014	Proportion of patients who received esmolol rescue when decrease heart rate $\leq 10\%$ at 5 min with landiolol

The clinical trials relied upon for assessment of effectiveness and safety included 6 randomized placebo-controlled trials and 2 randomized active-controlled trials with diltiazem and digoxin. The clinical trial populations were compared to the extent that detail was provided, and the differences in their dosing schemes and treatment benefits were compared qualitatively. Because clinical data was only submitted as published literature, without individual patient-level data, no auxiliary analyses including no quantitative global assessment of effectiveness, could be undertaken. For the published clinical trials, no meta-analysis was performed because the “publications of clinical studies (with only treatment group level granularity) used to support efficacy for the target indication have markedly different characteristics.” Thus, the primary comparative effectiveness demonstrated for landiolol hydrochloride on proposed post-hoc endpoint will be presented for each clinical trial in addition to the published primary endpoint from each trial, and the overall effectiveness of the agent will be assessed based on the cumulative qualitative weight of the findings from each of the individual clinical trials.

Reviewer Comment: Although initially requested and planned during the pre-NDA discussions with the Division, we agree with the applicant that meta-analysis could not be successfully undertaken with these data given their heterogeneity of populations, treatments, and outcome definitions.

Reviewer Comment: Although the absence of publication bias cannot be assured, in other words that there may have been other randomized controlled clinical trials performed with landiolol

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

that may not have supported the presence of a treatment effect of landiolol on HR, a review of the literature did not reveal any other clinical trial data. Given the number of clinical trials performed by diverse author groups at multiple institutions and unconnected with the current applicant it appears reasonable to presume that other data have not been purposefully hidden from publication.

Data regarding safety was also only able to be extracted from the submitted published literature without individual patient-level data. At least some adverse events were captured within each clinical trial, but the extent to which the clinical trial staff sought out adverse events or to what extent there may have been incomplete ascertainment is unknown. In addition, hypotension is a known consequence of beta-adrenergic receptor antagonists, but the definitions used for hypotension varied between the submitted trials, if it was reported at all, and change in blood pressure with treatment was only captured in some of the clinical trials. Nonetheless, the clinical trial data was qualitatively assessed, and that assessment was aided by the extensive post-marketing experience from the European Union and Japan to derive a more complete assessment of the safety of landiolol.

Although the formulations of landiolol hydrochloride are not identical between each of the clinical trials that were submitted as evidence for safety and effectiveness, based on communication with the clinical pharmacology reviewers, each formulation of landiolol was treated as interchangeable for the basis of the clinical review.

Note to the reader: Throughout this review the clinical trials taken from the published literature are referred to by their first author or authors names and the year of publication, so as to maintain consistency with the submitted information packet from the sponsor and the published literature.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Kato et al. 1997.

6.1.1. Study Design

Overview and Objective

Citation: Kato K, Hayakawa H, Atarashi H, et al. Clinical effect of intravenous infusion of landiolol hydrochloride (ONO-1101) on paroxysmal atrial fibrillation and atrial flutter – A phase III double-blind study in comparison with placebo. *Rinsho Iyaku (Jpn. J. Clin. Therap. Med.)* 1997b;13(19):4903(83)-4924(104).

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

A randomized placebo-controlled double-blind multi-center parallel clinical trial of landiolol hydrochloride as ONO-1101, in patients with non-perioperative paroxysmal AF and AFL, to assess safety and effectiveness of landiolol for control of heart rate (HR) over 11 minutes of administration and 15 minutes of post-administration monitoring.

Trial Design

Kato et al. 1997 is a randomized placebo-controlled double-blind multi-center parallel clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Kato et al. 1997 was performed at 57 centers in Japan from 1994 through 1997. Although completed entirely outside of the US, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Kato et al. 1997 enrolled consented patients with AF and AFL diagnosed within the prior 2 week and sustained for ≥ 5 minutes, and a HR >100 bpm, with age 16-75 years, and weight <90 kg. A central ECG assessment committee comprised of 2 physicians adjudicated the ECG diagnosis and type of arrhythmia in all cases. Patients were excluded if they had a myocardial infarction within 1 month, NYHA class III or IV heart failure, known second or third-degree atrioventricular heart block, sick sinus syndrome, blood pressure $\leq 100/70$ mmHg, or tachycardia that was felt by the treating clinician to be due to non-cardiac and non-thyroid disease such as anemia or infection. Patients who were pregnant or lactating, and those that had 'severe' liver, kidney, or blood disorders were also excluded. Patients were continuously monitored for the 5 minutes prior, during, and for the 15 minutes after drug administration.

Although the diagnostic criteria for AF and AFL are not documented in the submitted trial materials, these are clinically common and have typical non-ambiguous electrocardiographic findings that can be reasonably expected to have been made by the clinical teams treating these patients. The time frame of diagnosis described in the trial report establishes what is meant by 'paroxysmal,' or occurring for less than 2 weeks and for at least 5 minutes. Although this definition is not aligned with the definition of paroxysmal in the US guidelines, in which paroxysmal is defined as "AF that terminates spontaneously or with intervention within 7 days of onset," whereas persistent AF is defined as "continuous AF that is sustained >7 days," the enrolled trial population and duration of AF and AFL is sufficiently well-defined.¹⁶ Exclusion of

¹⁶ January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landiolol hydrochloride

patients >75 years of age appears unnecessary, as these patients are likely to be treated with landiolol, if approved. 'Severe' liver, kidney, and blood disorders are not defined, but given the hepatic metabolism of landiolol its use in patients with hepatic impairment will require further assessment. It is not clear why patients with renal dysfunction should be excluded from the clinical trial population given the limited renal clearance of the drug or its metabolites. If patients had received a previous antiarrhythmic medication prior to trial enrollment, that prior drug was discontinued and landiolol was not administered until the prior drug had been discontinued for a duration of at least 2 of its half-lives. Patients were prohibited from receiving concomitant antiarrhythmic medications including other beta-adrenergic receptor antagonists, calcium channel antagonists, intravenous digitalis, or sympathomimetics, but chronic oral digitalis formulations were allowed to be continued. These medication exclusions are reasonable from a clinical standpoint.

Kato et al. 1997 used weight-based landiolol hydrochloride dosing, with an intravenous loading dose of 250 mcg/kg over 1 minute, then a continuous infusion at 80 mcg/kg/min for 10 minutes. Landiolol was reconstituted in normal saline, which was used as the placebo arm infusion. Administration of the study medication could be discontinued at the discretion of the physician in charge if the SVT paroxysm terminated, there was 'marked bradycardia or hypotension', worsening tachycardia or overall patient condition, severe adverse events, or withdrawal of consent. Electrocardiographic and blood pressure monitoring was performed at each of the specified timepoints in Figure 1.

Figure 1. Kato et al. 1997 Schedule of Events¹⁷

American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014 Dec 2;130(23):2071-104.

¹⁷ Kato K, Hayakawa H, Atarashi H, et al. Clinical effect of intravenous infusion of landiolol hydrochloride (ONO-1101) on paroxysmal atrial fibrillation and atrial flutter – A phase III double-blind study in comparison with placebo. *Rinsho Iyaku (Jpn. J. Clin. Therap. Med.)* 1997b;13(19):4903(83)-4924(104).

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Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

In the case of Kato et al. 1997, the reported primary endpoint for the original clinical trial was an ordinal scale of a reduction in patient HR occurring within the monitored follow up period described in Figure 1. This ordinal scale was:

- 1: Substantially improved (paroxysm terminated and normal sinus rhythm restored or heart rate reduction $\geq 30\%$)
- 2: Moderately improved (paroxysm terminated intermittently or heart rate reduction $\geq 20\%$)
- 3: Slightly improved (heart rate reduction $< 20\%$)
- 4: No change (state of paroxysm unchanged or heart rate change $< 10\%$)
- 5: Worsened (heart rate increase $\geq 10\%$)

Following treatment, a central ECG assessment committee comprised of 2 physicians adjudicated the ECG response to treatment.

Reviewer Comment: In the case of the evidence assessment for the landiolol application, the reported primary endpoint for the published trial aligned with the proposed post-hoc endpoint for the overall evidence assessment.

Secondary endpoints included improvement in subjective arrhythmia symptoms on an ordinal scale, overall subjective symptom improvement on an ordinal scale, safety on an ordinal scale, and usefulness based on clinician subjective assessment on an ordinal scale. The utilized clinical outcome assessments were not accompanied by validation documentation, but the arrhythmia symptom assessment and overall symptomatic improvement have face validity similar to a patient global assessment of change. The ordinal scale for improvement in subjective arrhythmia symptoms was:

- 0: No symptom(s) during the entire observation period
- 1: Substantially improved
- 2: Moderately improved
- 3: Slightly improved
- 4: No change
- 5: Worsened

The ordinal scale for overall improvement was:

- 1: Substantially improved
- 2: Moderately improved
- 3: Slightly improved
- 4: No change
- 5: Worsened

Statistical Analysis Plan

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Mitchell Psozka, MD PhD
NDA 217202
Landiolol hydrochloride

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. The sponsor evaluated the potential of a meta-analysis, however substantial study heterogeneity prevented a meta-analytic approach. Given these limitations, no formal statistical hypothesis testing methodology was employed regarding the overall evidence for benefit. Agreement on this approach was reached with the Division prior to NDA submission.

Protocol Amendments

No protocol amendments to the published trial were reported.

6.1.2. Study Results

Compliance with Good Clinical Practices

The publication states that “The trial was conducted in compliance with Good Clinical Practice (GCP) guidelines after approval by the respective Institutional Review Boards (IRBs) of the participating study centers.”

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication.

Table 4. Kato et al. 1997 Patient Disposition²⁰

Analysis Set	Landiolol	Placebo	Total
Randomized	52	56	108
Discontinued after randomization (refer to Table 5 for reasons for exclusion)	2	7	9
Safety analysis set	50	49	99

²⁰ 1.11.3 – Clinical Information Amendment

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Primary efficacy endpoint analysis (improvement in HR) - Per-protocol set (PPS)	45	44	89
Excluded from the primary efficacy endpoint analysis (refer to Table 5 for reasons for exclusion).	5	5	10

Table 5. Reasons for patient exclusion from Kato et al. 1997

Reason for Discontinuation/Exclusion		Landiolol	Placebo	Total
Discontinued after randomization	Study medication not administered	2	6	8
	GCP violation (study medication administration outside trial period)	0	1	1
Excluded from the analysis	Heart rate before administration <80 bpm	3	2	5
	Heart rate before administration <80 bpm; adverse events observed	0	1	1
	Protocol violation (coadministration of disallowed drugs)	0	2	2
	Heart rate unstable	1	0	1
	No ECG	1	0	1

Protocol Violations/Deviations

Protocol deviations reported in the trial publication include, as reported in Table 5, do not appear sufficient to affect the overall conclusions of the study on the primary post-hoc endpoint:

- (1) 8 cases where the study medication was not administered after dissolution because the arrhythmia had terminated (2 in group A and 6 group P) were completely excluded.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

- (2) One case (from group P) was completely eliminated due to a GCP violation (administration outside the trial period).
- (3) Five cases with a pre-administration heart rate <80 bpm (3 cases in group A and 2 cases in group P) were included in the analysis of safety only.
- (4) One case (group P) with a pre-administration heart rate <80 bpm was included in the analyses of safety and usefulness only.
- (5) One case which had a heart rate of 83 bpm 5 minutes before administration and an unstable and highly variable heart rate just before administration (group A) was included in the analyses of safety and of improvement in subjective symptoms only.
- (6) Two cases where the study medication was administered within the 2x t_{1/2} exclusion window of a disallowed drug (one case had received pirlmenol 1 hour 26 minutes before and one case had received verapamil 2 hours 11 minutes earlier (both group P)) were included in the analysis of safety only.
- (7) One case where the values of the case report form could not be confirmed due to a lost ECG recording (group A) was included in the analyses of safety and of improvement in subjective symptoms only.

Table of Demographic Characteristics

The distribution of the baseline characteristics of the 99 cases included in the Kato et al. 1997 analyses are taken directly from the publication. No additional demographic data was submitted for these patients. No missing data were identified in the submitted publication.

Table 6. Demographic characteristics of the primary effectiveness analysis from Kato et al. 1997

Baseline factors		Treatment Group		Total	Test
		A	P		
Gender	M	29	35	64	N.S. ¹⁾ p=0.2352
	F	21	14	35	
Age (years)	21-55	15	11	26	N.S. ²⁾ p=0.5921
	56-65	13	15	28	
	66-70	7	11	18	
	71-75	12	10	22	
	76-83	3	2	5	
	Mean ± S.D.	60.9 ± 12.7	62.8 ± 9.9	61.9 ± 11.4	
Body weight (kg)	40-<50	9	5	14	N.S. ²⁾ p=0.3034
	50-<60	18	20	38	
	60-<70	16	17	33	
	70-85	7	7	14	
		Mean ± S.D.	59.5 ± 9.0	61.6 ± 9.9	
Treatment type	Hospitalized	36	32	68	N.S. ¹⁾ p=0.6162
	Outpatient	14	17	31	
Diagnosis	PAF	39	40	79	N.S. ¹⁾ p=0.8417
	PAFL	11	9	20	
Other arrhythmia	No	49	44	85	N.S. ¹⁾ p=0.4096
	Yes	9	5	14	
Duration of the illness	<1 month	9	14	23	N.S. ²⁾ p=0.5908
	1 month- 1 year	9	7	16	
	1 -5 years	12	14	26	
	>5 years	14	11	25	
	Unknown	6	3	9	
Type of onset	Natural onset	49	45	94	N.S. ³⁾ p=0.2044
	Triggered onset	1	4	5	
Comorbidity	No	17	16	33	N.S. ¹⁾ p=1.0000
	Yes	33	33	66	
NYHA class	I	44	43	87	N.S. ¹⁾ p=1.0000
	II	6	6	12	
Comedication	No	41	32	73	† ¹⁾ p=0.0972
	Yes	9	17	26	
Heart rate before administration (bpm)	60-79	3	3	6	N.S. ²⁾ p=0.7211
	80-99	12	10	22	
	100-119	13	10	23	
	120-139	11	16	27	
	140-183	11	10	21	
	Mean ± S.D.	116.9 ± 28.4	117.6 ± 23.3	117.3 ± 25.8	
Systolic blood pressure before administration (mmHg)	88-100	3	6	9	N.S. ²⁾ p=0.9462
	101-120	21	16	37	
	121-140	16	16	32	
	141-178	9	11	20	
	Unknown	1	0	1	
	Mean ± S.D.	125.4 ± 20.0	125.5 ± 21.4	125.4 ± 20.6	
Diastolic blood pressure before administration (mmHg)	50-70	13	12	25	N.S. ²⁾ p=0.5526
	71-80	13	11	24	
	81-90	15	16	31	
	91-120	8	10	18	
	Unknown	1	0	1	
	Mean ± SD	80.1 ± 14.1	81.3 ± 12.7	80.7 ± 13.4	
Time lag between onset of paroxysm and start of administration	<6 h	19	16	35	N.S. ²⁾ p=0.6101
	6 h-<24 h	13	13	26	
	24 hr - <2 wk	15	14	29	
	≥2 wk	3	3	6	
	Unknown	0	3	3	

¹⁾ χ^2 test; ²⁾ Wilcoxon's rank-sum test; ³⁾ Fisher's exact test; N.S.: not significant; †: $p < 0.15$

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the including patients was included in the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any use of potential rescue medications are not reported in the Kato et al. 1997 publication.

Efficacy Results – Primary Endpoint

In Kato et al. 1997 a substantially greater proportion of patients achieved the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or an achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently with landiolol treatment than with placebo. Unfortunately, only the per-protocol analysis is available in the publication, and the full (intention to treat or treatment policy) analysis set cannot be calculated. The per-protocol analysis is displayed in Table 7. The full breakdown from the publication is displayed in Table 8, recalling that moderate improvement is a decrease in HR of $\geq 20\%$ and a substantial improvement is a decrease in HR $\geq 30\%$ or restoration of sinus rhythm, and that A=landiolol and P=placebo in the table. Twenty-seven (60%) of the 45 landiolol-treated patients, compared to 1 of the 44 placebo-treated patients achieved the primary endpoint between 11 to 26 minutes after initiation of treatment.

Although the primary endpoint is a composite of HF reduction and termination of arrhythmia, few patients had termination of their arrhythmia. No patients treated with placebo had resolution of the arrhythmia, and in the landiolol-treated group 2 patients (4%) had permanent termination and 3 patients (7%) had intermittent termination. These comprised only 5 of the 27 patients who had either HR reduction or termination with landiolol in Kato et al. 1997. In addition, with both arrhythmia termination and HR reduction, the results with landiolol treatment were directionally similar for both components of the composite endpoint.

Table 7. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Kato et al. 1997

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving at Least Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Kato et al. 1997b	Not reported	Not reported	60% (n = 45)	2% (n = 44)	Not applicable. Full-Analysis Set not reported.

Table 8. Decrease in heart rate with landiolol treatment in Kato et al. 1997

Tmt Group	Substantially improved	Moderately improved	Slightly improved	No change	Worsened	Total	Assessment not possible	“Moderately improved” or better	Wilcoxon’s rank-sum test
A	12 (26.7%)	15 (33.3%)	11 (24.4%)	7 (15.6%)	0 (0%)	45 (100%)	0	27/45 (60.0%)	*** p=0.0001
P	0 (0%)	1 (2.3%)	4 (9.1%)	39 (88.6%)	0 (0%)	44 (100%)	0	1/44 (2.3%)	

***; $p < 0.001$

Based on the supplied table in the publication, there was no clear evidence of heterogeneity of treatment effect among

Landirolol hydrochloride

subpopulations of enrolled patients, displayed in Table 9 with A=landiolol and P=placebo. No other analyses of treatment heterogeneity were possible due to the lack of individual patient data.

Table 9. Subpopulation analysis of treatment effect in Kato et al. 1997

Baseline variable		Tmt Group	Substantially improved	Moderately improved	Slightly improved	No change	Worsened	Total	'Improved' (%)	Wilcoxon's rank-sum test
Gender	Male	A	5	8	8	4	0	25	52.0	***
		P	0	1	6	24	1	32	3.1	p=0.0001
	Female	A	6	9	2	3	0	20	75.0	***
		P	0	0	3	9	0	12	0.0	p=0.0001
Age (years)	≤65	A	4	8	8	4	0	24	50.0	***
		P	0	1	3	19	1	24	4.2	p=0.0001
	66-70	A	2	3	2	0	0	7	71.4	***
		P	0	0	3	8	0	11	0.0	p=0.0008
	≥71	A	5	6	0	3	0	14	78.6	***
		P	0	0	3	6	0	9	0.0	p=0.0033
Diagnosis	PAF	A	7	13	9	5	0	34	58.8	***
		P	0	1	9	25	1	36	8.8	p=0.0001
	PAFL	A	4	4	1	2	0	11	72.7	***
		P	0	0	0	8	0	8	0.0	p=0.0014
Duration of condition (years)	<1	A	4	6	3	2	0	15	66.7	***
		P	0	0	4	17	0	21	0.0	p=0.0001
	≥1	A	5	8	7	4	0	24	54.2	***
		P	0	1	4	14	1	20	5.0	p=0.0001
Concurrent illness	No	A	3	3	4	4	0	14	42.9	*
		P	0	1	4	11	0	16	6.3	p=0.0117
	Yes	A	8	14	6	3	0	31	71.0	***
		P	0	0	5	22	1	28	0.0	p=0.0001
NYHA class	I	A	10	15	8	6	0	39	64.1	***
		P	0	1	7	29	1	38	2.6	p=0.0001
	II	A	1	2	2	1	0	6	50.0	N.S.
		P	0	0	2	4	0	6	0.0	p=0.0512
Other medication before administration	No	A	6	5	6	5	0	22	50.0	***
		P	0	0	7	21	0	28	0.0	p=0.0001
	Yes	A	5	12	4	2	0	23	73.9	***
		P	0	1	2	12	1	16	6.3	p=0.0001
Comedication during administration	No	A	8	15	6	7	0	36	63.9	***
		P	0	1	7	23	0	31	3.2	p=0.0001
	Yes	A	3	2	4	0	0	9	55.6	***
		P	0	0	2	10	1	13	0.0	p=0.0001
Pre-administration heart rate (bpm)	≤99	A	1	5	3	2	0	11	54.6	**
		P	0	0	2	8	0	10	0.0	p=0.0028
	100-119	A	5	3	3	1	0	12	66.7	***
		P	0	0	1	9	0	10	0.0	p=0.0002
	≥120	A	5	9	4	4	0	22	63.6	***
		P	0	1	6	16	1	24	4.2	p=0.0001
Pre-administration systolic blood pressure (mmHg)	≤120	A	5	8	7	2	0	22	59.1	***
		P	0	0	3	15	0	18	0.0	p=0.0001
	≥121	A	5	9	3	5	0	22	63.6	***
		P	0	1	6	18	1	26	3.8	p=0.0001
Pre-administration diastolic blood pressure (mmHg)	≤80	A	5	8	6	4	0	23	56.5	***
		P	0	0	4	15	0	19	0.0	p=0.0001
	≥81	A	5	9	4	3	0	21	66.7	***
		P	0	1	5	18	1	25	4.0	p=0.0001
Time lag from onset of paroxysms to initiation of administration (h)	<6	A	5	6	2	3	0	16	68.8	**
		P	0	1	5	8	1	15	6.7	p=0.0011
	6 - <24	A	4	2	4	2	0	12	50.0	***
		P	0	0	2	11	0	13	0.0	p=0.0005
	≥24	A	2	9	4	2	0	17	64.7	***
		P	0	0	2	12	0	14	0.0	p=0.0001

N.S.: not significant, * : p < 0.05, ** : p < 0.01, *** : p < 0.001

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Based on the clinical trial publication there were not missing data from the per-protocol analysis, but the full intention to treat analysis set was not available. The lack of a treatment policy or intention to treat analysis does limit the validity of the data set, however of the 9 cases excluded from the per-protocol analysis, if all 7 of the unaccounted-for patients in the placebo arm had at least 20% reduction in HR and none of the 2 unaccounted-for patients in the landiolol arm had at least 20% HR reduction, then the proportion of landiolol-treated patients achieving the primary endpoint would be 27 out of 47, or 57.4% and the proportion of the placebo-treated patients achieving the primary endpoint would be 8 out of 51, or 15.7%. This sensitivity analysis supports the strength of the treatment effect despite the per-protocol analysis reported in the publication.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

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Data Quality and Integrity

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

Efficacy Results – Secondary and other relevant endpoints

In Kato et al. 1997, most of the secondary endpoints are only reported for the per-protocol analysis, not the treatment policy estimand, and therefore are not included here. The treatment policy (intention to treat) is reported for the overall subjective improvement endpoint, where A=landiolol and P=placebo, in Table 10. Patients treated with landiolol appeared to have overall improved symptoms and the specific improvement in symptoms is reported in Table 11.

Table 10. Overall subjective patient improvement in Kato et al. 1997

Tmt Group	Substantially improved	Moderately improved	Slightly improved	No change	Worsened	Total	Assessment not possible	“Moderately improved” or better	Wilcoxon’s rank-sum test
A	12 (24.0%)	17 (34.0%)	11 (22.0%)	8 (16.0%)	0 (0%)	50 (100%)	2 (4.0%)	29/50 (58.0%)	*** p=0.0001
P	0 (0%)	1 (2.0%)	9 (18.4%)	38 (77.6%)	1 (2.0%)	49 (100%)	0	1/49 (2.0%)	

***: $p < 0.001$

Table 11. Changes in subjective symptoms in Kato et al. 1997

Symptom	Tmt group	Change				Total	Improvement ≥ 1 level (%)	Wilcoxon’s rank-sum test
		+2 levels	+1 level	No change	-1 level			
Palpitation	A	9	11	7	0	27	74.1	*
	P	5	6	16	0	27	40.7	
Feeling of arrhythmia	A	5	9	7	0	21	66.7	*
	P	2	7	16	0	25	36.0	
Feeling of chest tightness	A	3	3	1	1	8	75.0	N.S. p=0.1636
	P	1	1	6	0	8	25.0	
Difficulty in breathing	A	1	4	4	0	9	55.6	-
	P	1	0	1	0	2	-	
Chest pain	A	1	3	0	0	4	-	-
	P	0	0	1	0	1	-	

N.S.: not significant, *: $p < 0.05$

Durability and Persistence of Response

Change in HR was captured at the specified time points in Kato et al. 1997, and the effect appeared durable during the 11 minutes of continuous administration, as depicted in Table 12 and Figure 2. Durability and persistence of heart rate response to landiolol in Kato et al. 1997. The HR effect of landiolol was also persistent up to 15 minutes after completion of landiolol infusion. HR reduced by 17% at 6 minutes of administration and by 20% by 11 minutes

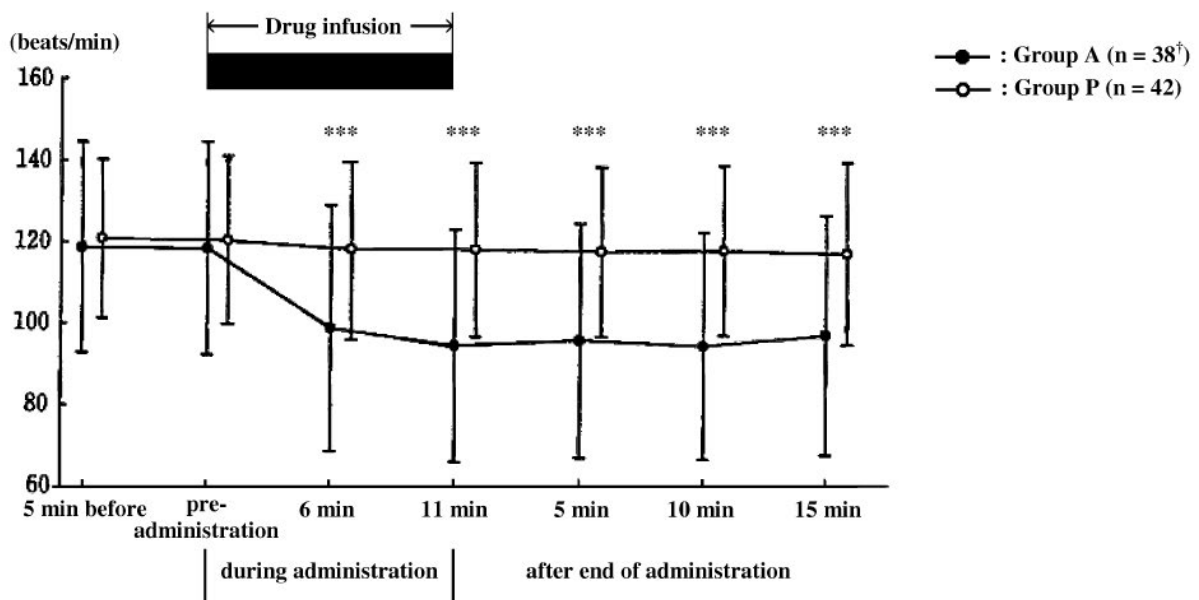
Clinical Review
 Mitchell Psofka, MD PhD
 NDA 217202
 Landiolol hydrochloride
 of administration.

Table 12. Durability of heart rate response to landiolol in Kato et al. 1997

Time point of measurement	Group A (n = 38)		Group P (n = 42)		Between-group comparison
	Actual value (bpm)	Relative change (%)	Actual value (bpm)	Relative change (%)	
Pre-administration	118.4 ± 26.0	-	120.3 ± 20.6	-	-
6 th minute	98.8 ± 30.2	-16.8 ± 13.4	118.2 ± 22.2	-1.9 ± 5.9	*** p=0.0001 ¹⁾
11 th minute	94.5 ± 28.6	-20.3 ± 13.2	118.0 ± 21.3	-1.8 ± 7.1	*** p=0.0001 ¹⁾
5 min after end	95.6 ± 28.7	-19.2 ± 14.0	117.3 ± 20.8	-2.2 ± 7.6	*** p=0.0001 ²⁾
10 min after end	94.2 ± 27.8	-20.2 ± 13.8	117.6 ± 20.8	-2.1 ± 7.1	*** p=0.0001 ²⁾
15 min after end	96.9 ± 29.4	-18.2 ± 14.1	116.7 ± 22.3	-3.0 ± 8.1	*** p=0.0001 ²⁾

Mean ± S.D., relative changes (%) compared to pre-administration values (t-test with Bonferroni correction until 11 min)
¹⁾***: p < 0.0005, ²⁾***: p < 0.001

Figure 2. Durability and persistence of heart rate response to landiolol in Kato et al. 1997



†: 5 min pre-administration values missing for three patients; ***: p < 0.0001

Additional Analyses Conducted on the Individual Trial

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

6.2. Yoshiya et al. 1997

6.2.1. Study Design

Overview and Objective

Citation: Yoshiya I, Ogawa R, Okumura F, et al. Clinical evaluation of landiolol hydrochloride (ONO- 1101) on peri-operative supraventricular tachyarrhythmia- a phase III, double-blind study in comparison with placebo. Rinsho Iyaku (Jpn. J. Clin. Therap. Med.) 1997;13(19):4949(129)-4978(158).

A randomized placebo-controlled double-blind multi-center parallel clinical trial of landiolol hydrochloride as ONO-1101, in patients with perioperative tachycardia, to assess safety and effectiveness of landiolol for control of heart rate (HR) over 11 minutes of administration and 60 minutes of post-administration monitoring.

Trial Design

Yoshiya et al. 1997 is a randomized placebo-controlled double-blind multi-center parallel clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Yoshiya et al. 1997 was performed at 46 centers in Japan from 1995 through 1996. Although completed entirely outside of the US, similar to Kato et al. 1997, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Yoshiya et al. 1997 enrolled consented patients with a HR ≥ 100 bpm that required treatment according to the treating clinician, and patients had to have either pre-existing ischemic heart disease or hypertension, tachyarrhythmia due to endocrine disease, sustained tachycardia triggered by a surgical procedure or anesthesia, or tachycardia that was sustained after correcting precipitating causes such as hypovolemia or anesthesia. Tachycardia had to be sustained for ≥ 3 minutes if sinus rhythm and during anesthesia, or ≥ 1 minute if supraventricular tachycardia (SVT) during anesthesia. Age was required to be ≥ 20 years.

Patients were excluded if they had a myocardial infarction within 1 month, 'severe' heart failure otherwise undefined, known second or third-degree atrioventricular heart block, or sick sinus syndrome. Patients who were pregnant or lactating, and those that had 'severe' liver, kidney, or blood disorders were also excluded. Patients were continuously monitored for the 5 minutes prior, during, and for the 15 minutes after drug administration. *There was no exclusion for low blood pressure reported for the trial.*

Clinical Review
 Mitchell Psozka, MD PhD
 NDA 217202
 Landiolol hydrochloride

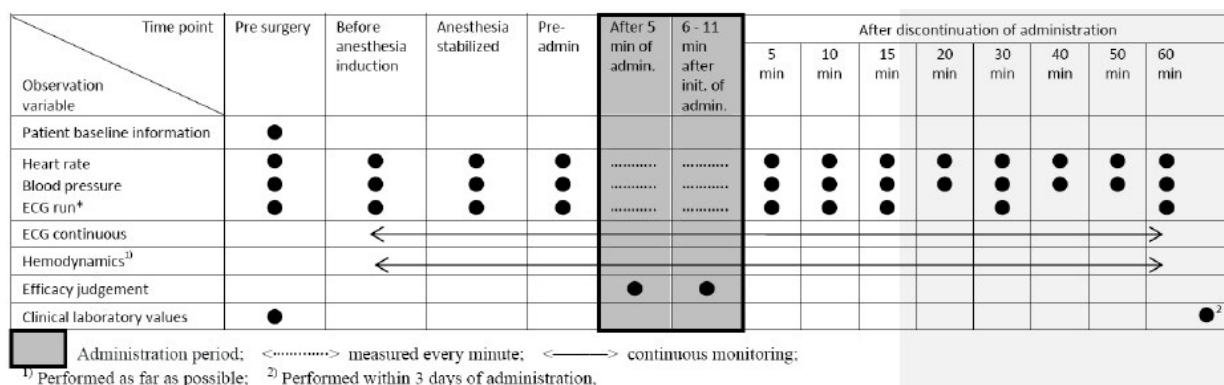
Yoshiya et al. 1997 used weight-based landiolol hydrochloride dosing, with an intravenous loading dose of 125 mcg/kg over 1 minute, then a continuous infusion at 40 mcg/kg/min for 10 minutes. This is half the loading and continuous infusion dose used in Kato et al. 1997. Landiolol was reconstituted in normal saline, which was used as the placebo arm infusion. Administration of the study medication could be discontinued at the discretion of the physician in charge if the SVT paroxysm terminated, there was ‘marked bradycardia or hypotension’, worsening tachycardia or overall patient condition, severe adverse events, or withdrawal of consent.

Patients were prohibited from receiving concomitant antiarrhythmic medications including other beta-adrenergic receptor antagonists, calcium channel antagonists, intravenous digitalis, or sympathomimetics, but chronic oral digitalis formulations were allowed to be continued. These medication exclusions are reasonable from a clinical standpoint.

The placebo and landiolol preparations were ensured to be indiscriminable, and “random allocation of the medication and concealment of the randomization codes” was performed. Two sets of samples picked out at random after patient allocation were analyzed by a third-party institution in Japan in order to confirm that the two preparations conformed to their respective specifications and were indiscriminable. Study medications (landiolol and placebo) were allocated according to random codes, stratified for each of the “high risk” (patients with pre-existing ischemic heart disease or hypertension) and the “low risk” subsets. The allocation codes and a separate set for emergency use were kept concealed until unblinding after database lock. Unblinding of the allocation codes was carried out after the database lock in the presence of the principal investigator and facilitators.

Electrocardiographic and blood pressure monitoring was performed at each of the specified timepoints in Figure 3. HR and BP were measured at a total of 23 time points: before surgery, before induction of anesthesia, after stabilization of anesthesia, immediately prior to administration, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 minutes after start of administration, 5, 10, 15, 20, 30, 40, 50, and 60 minutes after discontinuation of administration.

Figure 3. Yoshiya et al. 1997 Schedule of Events



Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

In Yoshiya et al. 1997, administration of the study medication could be discontinued at the discretion of the physician for adverse events, worsening tachyarrhythmia, ECG PQ time prolongation, bradycardia, or withdrawal of consent.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome.

In the case of Yoshiya et al. 1997, the reported primary endpoint for the original clinical trial was the rate of switch to rescue treatment if the HR reduction was $< 10\%$ after 7 minutes of treatment, and the next endpoint was an improvement in the tachyarrhythmia. For sinus tachycardia:

- 1: Substantially improved (heart rate reduction $\geq 30\%$)
- 2: Moderately improved (heart rate reduction $\geq 20\%$)
- 3: Slightly improved (heart rate reduction $< 20\%$)
- 4: No change (heart rate change $< 10\%$)
- 5: Worsened (heart rate increase $\geq 10\%$)

For supraventricular tachycardia (SVT):

- 1: Substantially improved (termination of paroxysm, restoration of normal sinus rhythm)
- 2: Moderately improved (intermittent termination of paroxysm or heart rate reduction $\geq 20\%$).
- 3: Slightly improved (heart rate reduction $< 20\%$)
- 4: No change (paroxysm unchanged or heart rate change $< 10\%$)
- 5: Worsened (heart rate increase $\geq 10\%$)

Secondary endpoints included usefulness based on clinician subjective assessment on an ordinal scale and safety assessment.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. In the published Yoshiya et al. 1997 trial, the patients labelled as high risk were analyzed separately from those labelled not as high risk. The primary endpoints were the rate of switch to rescue treatment (fraction of the cases discontinued due to an improvement rating of “no change” or “worsened”) after 7 minutes of infusion. As an additional statistical analysis, the rate of tachyarrhythmia improvement (sinus tachycardia and supraventricular arrhythmia) between the treatment groups (“moderately improved” or better) was compared using Wilcoxon’s rank-sum test with a

Clinical Review

Mitchell Psocka, MD PhD

NDA 217202

Landirolol hydrochloride

predefined alpha of 5% (two-sided). Intention to treat or a treatment policy estimand was utilized for all cases.

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.2.2. Study Results

Compliance with Good Clinical Practices

The text states that “The study was carried out in compliance with Good Clinical Practice (GCP) regulations after approval by the Institutional Review Board of each participating study center.”

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication.

Table 13. Yoshiya et al. 1997 Patient Disposition²¹

Analysis Set	Landiolol	Placebo	Total
Randomized	140	144	284
Discontinued after randomization (refer to Table 14 for reasons for exclusion)	4	5	9
Safety analysis set	136	139	275
Full-analysis set (FAS)	136	139	275

²¹ 1.11.3 – Clinical Information Amendment

Efficacy endpoint analysis (improvement in HR) - Per-protocol set (PPS)	117	127	244
Excluded from efficacy endpoint analysis (refer to Table 14 for reasons for exclusion)	19	12	31

Table 14. Reasons for patient exclusion from Yoshiya et al. 1997

Reason for Discontinuation/Exclusion		Landiolol	Placebo	Total
Discontinued after randomization	Study medication not administered	3	3	6
	Consistency between ECG and case report form not confirmed	1	2	3
Excluded from efficacy endpoint analysis	Pre-admin heart rate <100 bpm	1	1	2
	Incorrect dose	1	0	1
	Disallowed co-medication	10	8	18
	Discontinued despite improvement after 5 min	3	0	3
	Continued despite no change after 5 min and discontinued after 8 min due to insufficient drug solution	1	0	1
	Discontinued after 8 min due to insufficient drug solution	0	1	1
	Discontinued despite slight improvement after 5 min	1	2	3
	Discontinued due to adverse events	2	0	2

Protocol Violations/Deviations

Protocol deviations reported in the trial publication include, as reported in Table 14, do not appear sufficient to affect the overall conclusions of the study on the primary post-hoc endpoint:

- (1) 6 cases (3 cases in group A and in group P each) that did not receive study medication because the arrhythmia terminated before administration were completely excluded.

- (2) 3 cases (1 case in group A, 2 cases in group P) for whom an inconsistency between the ECG and the heart rate records could not be resolved due to improperly preserved ECG data were completely excluded.
- (3) 2 cases (1 case in group A and in group P each) in which the heart rate before administration was <100 bpm were included in the safety analysis only.
- (4) 1 case (group A) with incorrect dosing (11 minutes of loading dose) was included in the safety analysis only.
- (5) 18 cases (10 cases in group A, 8 cases in group P) that received comedICATIONS not allowed according to the study protocol (4 cases that received epinephrine 10 minutes before administration of study medication, 4 cases that were administered 0.5% xylocaine (lidocaine hydrochloride) with epinephrine (1:100,000) 10 minutes before administration of study medication, 2 cases that were administered atropine 10 minutes before administration of study medication, 1 case that was administered amrinone 12 minutes before administration of study medication, 1 case that was administered 10 mg of etilefrine 20 minutes before administration of study medication, 3 cases in whom the isoflurane concentration was changed by $\geq 3.5\%$, 1 case that was co-administered propofol, and 2 cases in whom the dosage of PGE1 was changed concomitant with the initiation of study medication administration) were included in the safety analysis only.
- (6) 3 cases (all in group A) in whom administration of study medication was discontinued after 6 minutes of administration despite a bradycardic effect of $\geq 10\%$ were included in the safety analysis only.
- (7) 2 cases were discontinued for non-medical reasons. Administration was continued despite “no change” after 5 minutes in 1 case in group A but discontinued after 8 minutes because there was not sufficient drug solution as it was spilled when a syringe was being filled in. This case was included in the safety analysis only. One patient in group P in whom administration was discontinued after 8 minutes due to insufficient drug solution (extension tube being too long causing a large dead volume) despite a bradycardic effect of $\geq 10\%$ after 5 minutes was included in the analyses of the rate of switch to rescue treatment (counted as “continued”) and safety.
- (8) 3 cases (1 case in group A, 2 cases in group P) in whom administration was discontinued after 5 minutes because the target heart rate was not achieved despite bradycardic effects of $\geq 10\%$ were included in the analyses of the rate of switch to rescue treatment (discontinued) and safety.
- (9) 2 cases (both in group A) in whom administration was discontinued due to adverse events (hypotension after 5 minutes and 6 minutes, respectively) were excluded from the analysis of the improvement of tachyarrhythmia.
- (10) 47 cases (9 cases in group A and 38 cases in group P) in whom administration was continued despite “no change” after 5 minutes were excluded from the analysis of the rate of switch to rescue treatment.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

Table of Demographic Characteristics

Table 15 shows the distribution of the baseline characteristics of the 275 cases included in the Yoshiya et al. 1997 analyses are taken directly from the publication. No additional demographic data was submitted for these patients. No missing data were identified in the submitted publication.

Most of the surgeries patients received were either head and neck region (37%) or abdominal region (38%) with 127 of the 275 patients (46%) identified as high risk based on the presence of ischemic heart disease or hypertension.

Whereas the Kato et al. 1997 trial enrolled patients with AF and AFL, Yoshiya et al. 1997 enrolled patients predominantly with sinus tachycardia (97%).

Table 15. Demographic characteristics of the primary effectiveness analysis from Yoshiya et al. 1997

Baseline characteristic	Treatment group	High risk		Test result	Low risk		Test result
		Group A	Group P		Group A	Group P	
Gender	Male	31	41	N. S. ¹⁾ p=0. 2692	39	43	N. S. ¹⁾ p=0. 4969
	Female	30	25		36	30	
Age (years)	21~39	3	1	N. S. ²⁾ p=0. 6498	23	26	N. S. ²⁾ p=0. 5080
	40~49	9	11		17	16	
	50~59	15	11		21	18	
	60~69	16	22		9	8	
	70~83	18	21		5	5	
Type of tachyarrhythmia	Sinus tachycardia	56	65	N. S. ³⁾ p=0. 1709	75	71	N. S. ³⁾ p=0. 2416
	Other	5	1		0	2	
Surgery site	Head/neck region	21	23	N. S. ³⁾ p=0. 5695	27	31	N. S. ³⁾ p=0. 3840
	Chest	4	10		5	9	
	Upper and lower abdomen	28	25		30	22	
	Bone/Joint	4	5		11	7	
	Other	4	3		2	4	
Duration of surgery (min)	30~ 119	12	6	† ²⁾ p=0. 0700	9	16	N. S. ²⁾ p=0. 1615
	120~ 239	23	23		26	30	
	240~ 359	19	22		19	13	
	360~1319	7	15		21	14	
Maintenance anesthetic	GOI	48	50	N. S. ¹⁾ p=0. 5385	55	53	N. S. ¹⁾ p=0. 9950
	GOS	9	8		14	14	
	Other	4	8		6	6	
Duration of anesthesia (min)	75~ 239	23	18	† ²⁾ p=0. 0730	24	23	N. S. ²⁾ p=0. 2255
	240~ 359	20	21		22	27	
	360~1385	18	27		29	23	
Time of onset of tachyarrhythmia	At intubation	11	6	N. S. ³⁾ p=0. 2164	8	6	N. S. ¹⁾ p=0. 8919
	At skin incision	12	12		13	12	
	During surgery	32	45		44	47	
	Other	6	3		10	8	
Complication	Ischemic heart disease	7	6	N. S. ³⁾ p=0. 5975	/	/	/
	Hypertension	50	58				
	Ischemic heart disease/hypertension	4	2				
Abnormal ECG findings	Absent	40	46	N. S. ¹⁾ p=0. 7592	71	69	N. S. ³⁾ p=1. 0000
	Present	21	20		4	4	
NYHA class	Normal	39	42	N. S. ²⁾ p=0. 9788	71	69	N. S. ²⁾ p=0. 7447
	I	18	20		4	3	
	II	3	3		0	0	
	Unknown	1	1		0	1	
Pre-admin heart rate (bpm)	78~105	25	36	† ²⁾ p=0. 1207	26	24	N. S. ²⁾ p=0. 6967
	106~115	16	20		33	29	
	116~162	20	10		16	20	
Pre-admin systolic blood pressure (mmHg)	71~109	10	13	N. S. ²⁾ p=0. 6140	22	24	N. S. ²⁾ p=0. 6577
	110~129	13	15		27	28	
	130~149	18	15		15	13	
	150~238	20	23		11	8	
Pre-admin diastolic blood pressure (mmHg)	31~ 59	7	9	N. S. ²⁾ p=0. 7574	15	17	N. S. ²⁾ p=0. 2810
	60~ 69	12	9		18	19	
	70~ 79	11	18		17	20	
	80~165	31	30		25	17	

¹⁾ χ^2 test; ²⁾ Wilcoxon's rank-sum test; ³⁾ Fisher's exact test; †: $p < 0.15$, N.S.: not significant

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the included patients was included in the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Yoshiya et al. 1997 publication.

Efficacy Results - Primary Endpoint

In Yoshiya et al. 1997 a substantially greater proportion of patients achieved the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or an achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently with landiolol treatment than with placebo, Table 16. Both the intention to treat and per-protocol analyses are consistent with the treatment effect of landiolol.

The primary endpoint from the trial publication, the rate of transition to rescue medication use for the tachyarrhythmia is displayed in Table 17, with A=landiolol and P=placebo. Overall, 15 of 136 patients were switched in the landiolol group (11%) and 68 of 139 patients were switched in the placebo group (49%).

The full breakdown in HR change from the publication is displayed in Table 18Table 8, recalling that moderate improvement is a decrease in HR of $\geq 20\%$ and a substantial improvement is a decrease in HR $\geq 30\%$ or restoration of sinus rhythm, and that A=landiolol and P=placebo in the table. One hundred seven (79%) of the 136 landiolol-treated patients, compared to 13 (9%) of the 139 placebo-treated patients achieved the primary endpoint between 11 to 71 minutes after initiation of treatment.

Table 16. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Yoshiya et al. 1997

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Yoshiya et al. 1997	79% (n = 136)	9% (n = 139)	80% (n = 117)	9% (n = 127)	No difference in response rates between Analysis Sets.

Table 17. Rate of switch to rescue treatment in Yoshiya et al. 1997

Population		Total (n)	Continued (n)	Switched (n)	Rate of change (%)	p value (χ^2 test)
Overall	A	136	121	15	11.0	***
	P	139	71	68	48.9	0.0001
High risk	A	61	55	6	9.8	***
	P	66	33	33	50.0	0.0001
Low risk	A	75	66	9	12.0	***
	P	73	38	35	48.0	0.0001

***: $p < 0.001$

Clinical Review
 Mitchell Psozka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 18. Decrease in heart rate with landiolol treatment in Yoshiya et al. 1997

Population		Total (n)	Substan- tially improved (n)	Modera- tely improved (n)	Slightly improved (n)	No change (n)	Wor- sened (n)	“Moderately improved” or better (%)	p value (Wilcoxon’s rank-sum test)
Overall	A	136	51	56	17	12	0	78.7	***
	P	139	4	9	26	98	1	9.4	0.0001
High risk	A	61	30	20	7	4	0	82.0	***
	P	66	2	2	13	47	1	6.1	0.0001
Low risk	A	75	21	36	10	8	0	76.0	***
	P	73	2	7	13	51	0	12.3	0.0001

***: $p < 0.001$

Based on the clinical trial publication there were not missing data from the intention to treat analysis.

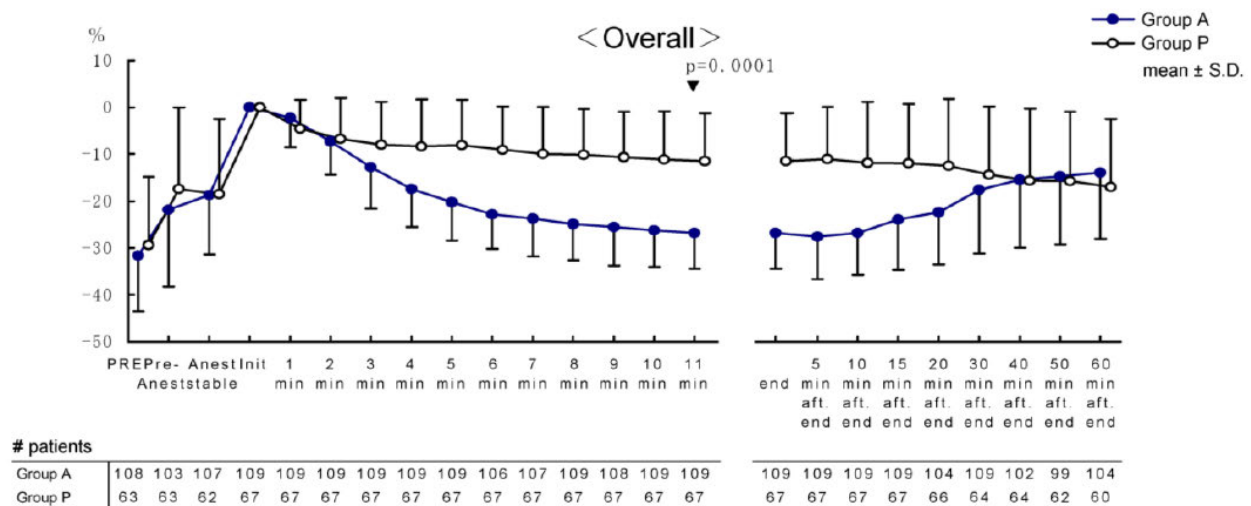
Data Quality and Integrity - Reviewers' Assessment

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

Durability and Persistence of Response

Change in HR was captured at the specified time points in Yoshiya et al. 1997, and the effect appeared durable during the 11 minutes of continuous administration for those patients who received all 11 minutes and were not switched, as depicted in Figure 4. The HR effect of landiolol was also persistent up to 15 minutes after completion of landiolol infusion. Overall, after 5 minutes of administration, the mean heart-rate reductions were 19.3% with landiolol and 5.3% with placebo. The mean bradycardic effect at 11 minutes of administration was 26.8% with landiolol and 11.5% with placebo. The heart rates 30 minutes after discontinuation of administration in the complete population were 91.6 ± 15.9 bpm in the landiolol group and 95.0 ± 15.4 bpm in the placebo group, without a significant between-group difference.

Figure 4. Durability and persistence of heart rate response to landiolol in Yoshiya et al. 1997



Additional Analyses Conducted on the Individual Trial

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

6.3. Yoshiya et al. 2002

6.3.1. Study Design

Overview and Objective

Citation: Yoshiya I, Ogawa R, Okumura F, et al. Clinical evaluation of landiolol hydrochloride (ONO- 1101) on peri-operative supraventricular tachyarrhythmia in patients with hypertension or cardiac ischemia– double-blind study in comparison with placebo. *Rinsho Iyaku (Jpn. J. Clin. Therap. Med.)*. 2002;18(9):1049(37)- 076(64).

A randomized placebo-controlled double-blind multi-center parallel clinical trial of landiolol hydrochloride as ONO-1101, in patients with perioperative tachycardia, to assess safety and effectiveness of landiolol for control of heart rate (HR) over 11 minutes of administration and 60 minutes of post-administration monitoring.

Trial Design

Yoshiya et al. 2002 is a randomized placebo-controlled double-blind multi-center parallel clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Yoshiya et al. 2002 was performed at 19 centers in Japan from 1998 through 2000. Although completed entirely outside of the US, similar to Kato et al. 1997 and Yoshiya et al. 1997, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL and supraventricular tachycardia are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Yoshiya et al. 2002 enrolled consented patients with a perioperative supraventricular tachycardia that required treatment according to the treating clinician, and patients had to have either pre-existing ischemic heart disease defined by prior myocardial infarction or angina requiring treatment, ischemic electrocardiographic or echocardiographic changes, or hypertension requiring antihypertensive treatment. If sinus tachycardia, HR had to be ≥ 120 bpm and had to be sustained for ≥ 3 minutes or HR ≥ 100 bpm with a rate-pressure product (RPP) $\geq 15,000$ bpm x mmHg for ≥ 3 minutes. Supraventricular or non-sinus tachycardia required HR ≥ 120 bpm for ≥ 1 minute. In all cases tachycardia was sustained after correction of known precipitating causes such as hypovolemia and anesthesia.

Patients were excluded if they had a myocardial infarction within 1 month, 'severe' heart failure with NYHA III or IV, known second or third-degree atrioventricular heart block, or sick sinus syndrome. Patients were also excluded if they had used a beta-adrenergic receptor antagonist within 1 week prior to surgery. Patients who were pregnant or lactating, and those that had

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202

Landirolol hydrochloride

liver, kidney, or blood disorders defined by AST ≥ 100 IU/L, ALT ≥ 100 IU/L, blood urea nitrogen ≥ 25 mg/dL, creatinine ≥ 2 mg/dL, or mucosal or gum bleeding of at least moderate degree within 1 week prior to surgery, were also excluded. Patients were continuously monitored for the 5 minutes prior, during, and for the 60 minutes after drug administration. *There was no exclusion for low blood pressure reported for the trial.*

Patients were prohibited from receiving concomitant antiarrhythmic medications including other beta-adrenergic receptor antagonists, calcium channel antagonists, digitalis, or sympathomimetics, or cholinesterase inhibitors. These medication exclusions are reasonable from a clinical standpoint.

Yoshiya et al. 2002 used weight-based landiolol hydrochloride dosing, with an intravenous loading dose of 125 mcg/kg over 1 minute, then a continuous infusion at 40 mcg/kg/min for 10 minutes. This is half the loading and continuous infusion dose used in Kato et al. 1997 and the same as the dose in Yoshiya et al. 1997. Landiolol was reconstituted in normal saline, which was used as the placebo arm infusion. Administration of the study medication could be discontinued at the discretion of the physician in charge if the SVT paroxysm terminated, there was 'marked bradycardia or hypotension', worsening tachycardia or overall patient condition, severe adverse events, or withdrawal of consent.

The placebo and landiolol preparations were ensured to be indiscriminable, and "random allocation of the medication and concealment of the randomization codes" was performed. Two sets of samples picked out at random after patient allocation were analyzed by a third-party institution in Japan in order to confirm that the two preparations conformed to their respective specifications and were indiscriminable. Study medications (landiolol and placebo) were allocated according to random codes, stratified for each of the "high risk" (patients with pre-existing ischemic heart disease or hypertension) and the "low risk" subsets. The allocation codes and a separate set for emergency use were kept concealed until unblinding after database lock. Unblinding of the allocation codes was carried out after the database lock in the presence of the principal investigator and facilitators.

Electrocardiographic and blood pressure monitoring was performed at each of the specified timepoints in Figure 5. These were measured at a maximum of 21 time points: before operation, before induction of anesthesia, after stabilization of anesthesia, 3 minutes before administration, immediately before administration, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 minutes after initiation of administration or at the time of discontinuation, 5, 10, 15, 30, and 60 minutes after discontinuation of administration.

Figure 5. Yoshiya et al. 2002 Schedule of Events

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome.

In the case of Yoshiya et al. 2002, the reported primary endpoint for the original clinical trial was an ordinal scale of a reduction in patient HR occurring within the monitored follow up period described in Figure 5Figure 1. This ordinal scale was:

- 1: Substantially improved (heart rate reduction $\geq 30\%$)
- 2: Moderately improved (heart rate reduction $\geq 20\%$)
- 3: Slightly improved (heart rate reduction $< 20\%$)
- 4: No change (state of paroxysm unchanged or heart rate change $< 10\%$)
- 5: Worsened (heart rate increase $\geq 10\%$)

Secondary endpoints included the rate of landiolol discontinuation, and change in HF, BP, and RPP.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. Intention to treat or a treatment policy estimand is reported for the trial results.

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.3.2. Study Results

Compliance with Good Clinical Practices

The publication states “The trial was conducted in compliance with Good Clinical Practice (GCP) guidelines (Ministry of Health and Welfare ordinance No. 28, dated 1997-03-27) after approval by the respective Institutional Review Boards (IRBs) of the participating study centers.”

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride
Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication.

Table 19. Yoshiya et al. 2002 Patient Disposition²²

Analysis Set	Landiolol	Placebo	Total
Randomized	29	29	58
Discontinued after randomization (refer to Error! Reference source not found. for reasons for exclusion)	2	2	4
Safety analysis set	27	27	54
Full-analysis set (FAS)	27	27	54
Excluded from Full-analysis set (FAS) (refer to Error! Reference source not found. for reasons for exclusion)	0	0	0
Primary efficacy endpoint analysis (improvement in HR) - Per-protocol set (PPS)	21	20	41
Excluded from Per-protocol set (PPS) (refer to Error! Reference source not found. for reasons for exclusion)	6	7	13

Table 20. Reasons for patient exclusion from Yoshiya et al. 2002

Reason for Discontinuation/Exclusion		Landiolol	Placebo	Total
Discontinued after randomization	Study medication not administered because tachycardia resolved before administration of study medication	2	2	4
Excluded from Per-protocol set (PPS)	Violation of inclusion criteria ($\geq 10\%$ change in heart rate pre-administration compared to 3 min before)	0	1	1

²² 1.11.3 – Clinical Information Amendment

	Violation of inclusion criterion (i) or (ii)*	4	2	6
	Violation of administration schedule (administration discontinued despite bradycardic effect $\geq 10\%$ within 5 min of administration)	0	2	2
	Violation of administration schedule (administration continued despite bradycardic effect $< 10\%$ within 5 min of administration)	1	2	3
	Protocol violation (coadministration of disallowed drugs after induction of anesthesia)	1	3	4

Protocol Violations/Deviations

There were no cases with GCP noncompliance. 1 case in which the change of the pre-administration heart rate was $\geq 10\%$ compared to 3 minutes before, and 6 cases that did not meet the inclusion criteria, i.e., a total of 7 cases, were excluded from the per-protocol analysis. Two cases for which the administration was discontinued despite bradycardic effects of $\geq 10\%$ within 5 minutes of administration, and 3 cases for which the administration was continued even though bradycardic effects were $< 10\%$ after 5 minutes of administration, were excluded from the per-protocol analysis as violations of the administration schedule. In addition, 4 cases where drugs not allowed according to the study protocol were administered after induction of anesthesia were excluded from the per-protocol analysis as well. There were 11 cases with violations of the administration schedule (1 vial of study medication was dissolved in 20 or 50 ml rather than 5 ml of physiological saline); these were all included in the analyses as the impact of the administered volume on hemodynamics was considered negligible.

Details of 5 cases with violations of the administration schedule: In 2 patients the administration was discontinued despite a bradycardic effect $\geq 10\%$. In patient 1-4 (landiolol group) a bradycardic effect $\geq 10\%$ was achieved within 5 minutes of administration, but the ST value 17 changed from -0.05 mV pre-administration to -0.1 mV after 1 minute of administration, and RPP after 5 minutes of administration was 16,906 bpm $\times$ mmHg (from a pre-administration value of 26,375 bpm $\times$ mmHg) indicating a sustained high cardiac workload in excess of 15,000 bpm $\times$ mmHg. The physician in charge therefore decided to discontinue administration. In patient 15-2 (landiolol group) administration was discontinued because the bradycardic effect was determined to be $< 10\%$ from the heart rate on the monitor (94 bpm) after 5 minutes of administration; the ECG record, however, showed a bradycardic effect of $\geq 10\%$ (87 bpm).

Details of 3 patients in whom the administration was continued even though bradycardic effects were <10% after 5 minutes of administration: Patient 7-1 (group placebo) had undergone coronary arterial revascularization and the bradycardic effect after 5 minutes of administration was <10%. However, the physician in charge decided to continue administration because there were no electrocardiographic indicators of myocardial ischemia and an RPP reduction by 30.7% (from 16,430 bpm · mmHg pre-administration to 11,385 bpm · mmHg) was apparent after 5 minutes of administration. Patient 21-1 (landiolol group) presented with left ventricular hypertrophy during preoperative examination and developed tachycardia during operation handling and the bradycardic effect after 5 minutes of administration was <10%. However, the physician in charge decided to continue administration because there were no electrocardiographic indicators of myocardial ischemia and RPP had decreased by 17.3% (from 17,120 bpm × mmHg pre-administration to 14,157 bpm × mmHg) after 5 minutes of administration despite continued high operative stress from nephrectomy. Patient 19-1 (landiolol group) had a complication of hypertension and a high heart rate of 120 bpm pre-surgery. The RPP changed from 19,320 bpm × mmHg before the operation to 17,402 bpm × mmHg immediately before administration. The bradycardic effect after 5 minutes of administration was <10%, however, there were no electrocardiographic indicators of myocardial ischemia and RPP had decreased to 15,594 bpm × mmHg (by 19.3% compared to before surgery and 10.4% compared to pre-administration) after 5 minutes of administration. The physician in charge concluded that the cardiac workload was on the way to being reduced and decided to continue administration.

Table of Demographic Characteristics

Table 21 shows the inclusion criteria med regarding cardiovascular risk factors and HR in the Yoshiya et al. 2002 trial. Close to half had hypertension, and half had ischemic changes on ECG on preoperative examination.

Table 21. Inclusion criteria met for Yoshiya et al. 2002

Inclusion criterion		Sinus tachycardia			Other than sinus tachycardia	Total
		a	b	a+b	c	
		Patients with heart rate ≥ 120 bpm sustained for ≥ 3 min Note 4)	Patients with heart rate ≥ 100 bpm and RPP $\geq 15,000$ bpm $\times$ mmHg sustained for ≥ 3 min		Patients with heart rate ≥ 100 bpm sustained for ≥ 1 min	
(i)	Patients with hypertension or a history thereof and have been treated with an antihypertensive drug	0	20	3	3	26 ¹⁾
	Patients with a history of myocardial infarction or have a complication of myocardial infarction and have been treated	1	1	0	0	2
	Patients with a history of angina and treatment	0	3	1	0	4
	Patients with ischemic changes on the ECG (resting or exercise) or echocardiography during preoperative examination	2	20	2	3	27 ²⁾
(ii)	Patients with heart rate ≥ 100 bpm sustained for ≥ 1 min and recent ST changes (≥ 0.1 mV) on the ECG accompanied by an increased heart rate	17				17

¹⁾ 3 patients that did not meet the inclusion criteria for heart rate and RPP values immediately pre-administration were excluded.

²⁾ Abnormal findings: 13 patients ECG only, 7 patients echocardiography only, 7 patients both ECG and echocardiography (3 patients, 1 patient, and 1 patient, respectively, that did not meet the inclusion criteria for heart rate and RPP values immediately pre-administration were excluded)

Table 22 shows the distribution of the baseline characteristics of the 54 cases included in the Yoshiya et al. 2002 analyses, taken directly from the publication. No additional demographic data was submitted for these patients. No missing data were identified in the submitted publication. A=landiolol, P=placebo. Most of the perioperative tachycardia occurred at the time of the surgical operation.

Clinical Review
 Mitchell Psofka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 22. Demographic characteristics from Yoshiya et al. 2002

Characteristic		Treatment Group		Test
		Group A	Group P	
Gender	Male	16	19	N.S. ¹⁾ <i>p</i> = 0.5687
	Female	11	8	
Age (years)	29-39	2	1	N.S. ²⁾ <i>p</i> = 0.7885
	40-49	14	13	
	60-88	11	13	
	29-64	21	17	
	65-88	6	20	
	Mean ± S.D.	58.3 ± 13.4	59.3 ± 14.6	
	Median [IQR]	58 [51; 64]	59 [49; 70]	
Body weight (kg)	33.0-49.9	6	3	N.S. ²⁾ <i>p</i> = 0.8967
	50.0-59.9	8	14	
	60.0-87.5	13	10	
	Mean ± S.D.	58.8 ± 12.7	59.3 ± 10.2	
	Median [IQR]	59 [50; 70]	57.8 [53; 63.95]	
Type of tachyarrhythmia	Sinus tachycardia	24	26	N.S. ¹⁾ <i>p</i> = 0.6104
	Paroxysmal atrial fibrillation	3	1	
Surgery site	Head/neck region	10	4	N.S. ¹⁾ <i>p</i> = 0.2534
	Chest	2	1	
	Upper and lower abdomen	13	16	
	Bone/joint	1	4	
	Other	1	2	
Duration of surgical procedure (min)	32-119	11	6	† ²⁾ <i>p</i> = 0.1236
	120-239	8	7	
	240-359	4	7	
	360-762	4	7	
	Mean ± S.D.	217.5 ± 196.1	255.1 ± 145.6	
	Median [IQR]	147 [85; 295]	275 [135; 360]	
Pre-administered drug	No	2	3	N.S. ¹⁾ <i>p</i> = 1.000
	Yes	25	24	
Duration of anesthesia (min)	55-239	18	12	N.S. ¹⁾ <i>p</i> = 0.1560
	240-359	3	7	
	360-808	6	8	
	Mean ± S.D.	251.6 ± 195.1	291.3 ± 148.4	
	Median [IQR]	185 [123; 340]	310 [165; 403]	
Type of maintenance anesthetic drug	GOI	17	21	N.S. ¹⁾ <i>p</i> = 0.4753
	GOS	4	2	
	Other	6	4	
Muscle relaxant drug	No	0	0	-
	Yes	27	27	
Time point of tachycardia onset	At the time of intubation	8	3	† ¹⁾ <i>p</i> = 0.1297
	At the time of skin incision	4	2	
	At the time of operation	15	20	
	Other	0	2	
Hypertension	No	7	11	N.S. ¹⁾ <i>p</i> = 0.3865
	Yes	20	16	
	History but no complication at the time of hospitalisation, antihypertensive drug not administered	3	4	
	History but no complication at the time of hospitalisation, antihypertensive drug administered	5	3	
	Complication since hospitalisation	10	7	
	Complication found during preoperative examination	2	2	

Clinical Review
 Mitchell Psocka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Myocardial infarction	No	26	26	N.S. ¹⁾ <i>p</i> = 1.000
	Yes	1	1	
	No complication at the time of start of administration	1	1	
	Complication present at the time of start of administration	0	0	
Angina	No	25	24	N.S. ¹⁾ <i>p</i> = 1.000
	Yes	2	3	
	No complication at the time of start of administration; no treatment given	1	1	
	Complication present at the time of start of administration; treatment given	0	0	
Abnormal findings in preoperative ECG	No	12	9	N.S. ¹⁾ <i>p</i> = 0.5766
	Yes	25	18	
	Resting			
	ST	8	6	
	T wave	5	10	
	abnormal Q wave	3	1	
	U wave	0	0	
	Other	8	12	
	Exercise			
	ST	3	0	
	T wave	0	0	
	abnormal Q wave	0	0	
	U wave	0	0	
	Other	0	0	
Abnormal finding in echocardiography	No	6	2	N.S. ¹⁾ <i>p</i> = 0.2108
	Yes	7	9	
	Not available	14	16	
Co-medication	No	14	11	N.S. ¹⁾ <i>p</i> = 0.5852
	Yes	13	16	
Preoperative NYHA status	Normal	12	13	N.S. ²⁾ <i>p</i> = 0.5959
	I	13	14	
	II	2	0	
Time lag between onset of arrhythmia and start of administration (min)	1-5	12	12	N.S. ²⁾ <i>p</i> = 0.7536
	6-10	12	9	
	11-25	3	4	
	26-30	0	2	
	Mean ± S.D.	6.7 ± 3.8	9.3 ± 8.3	
	Median [IQR]	6 [4; 8]	6 [3; 10]	
Pre-administration heart rate (bpm)	97-105	8	13	N.S. ²⁾ <i>p</i> = 0.1965
	106-110	7	1	
	111-115	4	8	
	116-120	2	2	
	121-129	6	3	
	Mean ± S.D.	112.1 ± 9.3	109.3 ± 8.2	
Median [IQR]	109 [106; 120]	107 [102; 113]		
Pre-administration systolic blood pressure (mmHg)	86-109	1	3	N.S. ²⁾ <i>p</i> = 0.9036
	110-129	2	1	
	130-149	5	3	
	150-159	5	3	
	160-179	6	10	
	180-211	8	7	
Mean ± S.D.	161.4 ± 26.9	158.2 ± 32.6		
Median [IQR]	165 [145; 181]	163 [136; 181]		
Pre-administration diastolic blood pressure (mmHg)	48-59	1	2	N.S. ²⁾ <i>p</i> = 0.8899
	60-69	1	0	
	70-79	3	4	
	80-89	3	2	
	90-99	7	9	
	100-137	12	10	

Clinical Review
 Mitchell Psofka, MD PhD
 NDA 217202
 Landiolol hydrochloride

	Mean ± S.D. Median [IQR]	95.2 ± 18.1 99 [81; 105]	95.1 ± 21.3 94 [81; 107]	
Pre-administration rate pressure product (bpm×mmHg)	9506-11,999	0	4	N.S. ²⁾ <i>p</i> = 0.3966
	12,000-14,999	4	0	
	15,000-17,999	9	12	
	18,000-20,999	8	8	
	21,000-26,375	6	3	
	Mean ± S.D. Median [IQR]	18,073.8 ± 3222.5 18,100 [15,500; 20,458]	17,277.6 ± 3816.0 17,238 [15,450; 19,482]	
Pre-operative ST value (mV) ³⁾	0-0.049	11	15	N.S. ²⁾ <i>p</i> = 0.1902
	0.05-0.099	5	4	
	0.1-0.6	11	6	
	Not available	0	2	
		Mean ± S.D. Median [IQR]	0.077 ± 0.089 0.05 [0; 0.10]	

¹⁾ χ^2 test (Fisher's exact test); ²⁾ Wilcoxon's rank-sum test; ³⁾ counted from absolute values; †: *p* < 0.15; N.S.: not significant

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the included patients was included in the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Yoshiya et al. 2002 publication.

Efficacy Results - Primary Endpoint

In Yoshiya et al. 2002 a substantially greater proportion of patients achieved the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or an achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently with landiolol treatment than with placebo, Table 23. Both the intention to treat and per-protocol analyses are consistent with the treatment effect of landiolol.

The primary endpoint from the clinical trial publication, the proportion of patients that had improvement in HR is displayed in Table 24, recalling that moderate improvement is a decrease in HR of $\geq 20\%$ and a substantial improvement is a decrease in HR $\geq 30\%$ or restoration of sinus rhythm, and that A=landiolol and P=placebo in the table.

The full breakdown in HR change up to 5 minutes of administration is displayed in Table 25.

Table 23. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Yoshiya et al. 2002

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Yoshiya et al. 2002	89% (n = 27)	11% (n = 27)	86% (n = 21)	10% (n = 20)	No difference in response rates between Analysis Sets.

Table 24. Decrease in heart rate with landiolol treatment in Yoshiya et al. 2002

Admin Group	Substantially improved	Moderately improved	Slightly improved	No change	Worsened	Total	“Moderately improved” or better	χ^2 test	Wilcoxon’s rank-sum test
A	17	7	0	1	2	27	24/27 (88.9%)	*** $p = 0.0001$	*** $p = 0.0001$
P	1	2	3	21	0	27	3/27 (11.1%)		

***: $p < 0.001$

Table 25. Change in heart rate up to 5 minutes of administration in Yoshiya et al. 2002

	Group A			Group P			<i>t</i> -test for relative change
	Actual measurement value (bpm; mean ± S.D.)	Δ (relative change) (%; mean ± S.D.)	<i>n</i>	Actual measurement value (bpm; mean ± S.D.)	Δ (relative change) (%; mean ± S.D.)	<i>n</i>	
Pre-administration	113.2 ± 10.0	-	21	107.5 ± 6.7	-	20	***; <i>p</i> = 0.001
At discontinuation of administration	75.4 ± 11.8	-33.0 ± 9.7	21	103.6 ± 13.1	-3.7 ± 9.9	20	
1 min of administration	110.1 ± 15.1	-3.0 ± 7.7	21	106.1 ± 8.0	-1.3 ± 4.7	20	N.S.; <i>p</i> = 0.4086
2 min of administration	103.0 ± 16.1	-9.3 ± 9.8	21	105.0 ± 9.8	-2.4 ± 5.5	20	**; <i>p</i> = 0.0094
3 min of administration	93.2 ± 15.3	-17.8 ± 10.4	21	104.6 ± 11.4	-2.9 ± 6.7	20	***; <i>p</i> = 0.001
4 min of administration	85.0 ± 13.0	-25.0 ± 9.6	21	104.3 ± 12.0	-3.1 ± 8.1	20	***; <i>p</i> = 0.001
5 min of administration	81.1 ± 11.3	-28.3 ± 8.4	21	103.9 ± 12.0	-3.5 ± 8.5	20	***; <i>p</i> = 0.001

***; *p* < 0.001; **; *p* < 0.01; N.S.: not significant

Note: *t*-test was carried out for 1 minute to 5 minutes of administration using a closed testing procedure in the sequence “5 minutes of administration” to “4 minutes etc. until “to 1 minute of administration”.

Data Quality and Integrity - Reviewers' Assessment

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

Durability and Persistence of Response

Change in HR was captured at the specified time points in Yoshiya et al. 2002, and the effect appeared durable during the 11 minutes of continuous administration for those patients who received all 11 minutes and were not switched, as depicted in Figure 6. By 60 minutes after administration of landiolol and placebo had been discontinued, there was clinically small difference in HR between the treatment groups, as seen in Figure 6 and Table 26.

Figure 6. Durability and persistence of heart rate response in Yoshiya et al. 2002

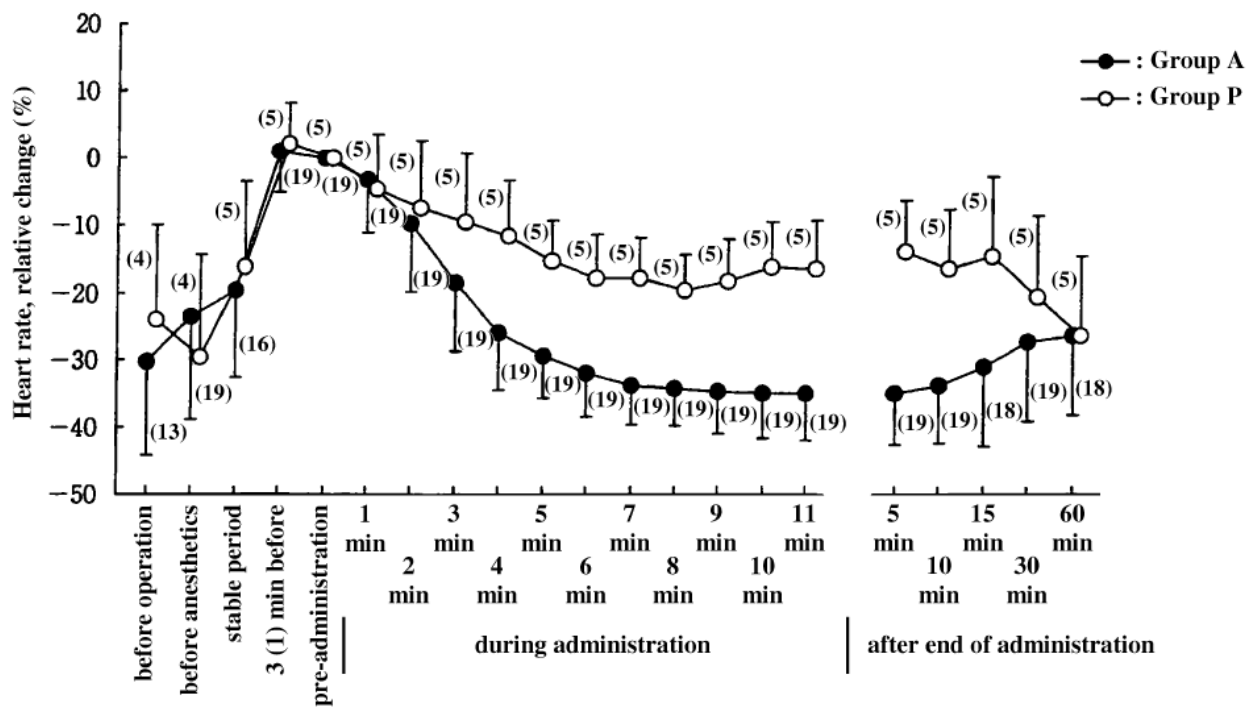


Table 26. Heart rates 30 and 60 minutes after discontinuation in Yoshiya et al. 2002

	Group A			Group P			t-test for relative change [95% CI for difference]
	Actual measurement value (bpm; mean ± S.D.)	Δ (relative change) (%; mean ± S.D.)	n	Actual measurement value (bpm; mean ± S.D.)	Δ (relative change) (%; mean ± S.D.)	n	
Pre-administration	113.2 ± 10.0	-	21	107.5 ± 6.7	-	20	
30 min after discontinuation of administration	82.5 ± 15.4	-27.2 ± 11.8	21	89.7 ± 9.1	-16.3 ± 9.8	20	**; p = 0.0027 [-17.5; -4.2]
60 min after discontinuation of administration	82.3 ± 12.9	-26.6 ± 11.2	21	86.0 ± 11.2	-20.0 ± 10.5	19	N.S.; p = 0.0667 [-13.4; 0.2]

**; p < 0.01; N.S.: not significant

Additional Analyses Conducted on the Individual Trial

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

6.4. Tanaka et al. 2008

6.4.1. Study Design

Overview and Objective

Citation: Tanaka S, Kikuchi C, Saito N, et al. Clinical evaluation of landiolol hydrochloride, an ultra short-acting betablocker. *Kyobu Geka (Jpn. J. Thorac. Surg.)* 2008;61(13):1096-1101.

A 12-patient randomized placebo-controlled double-blind single-center parallel treatment clinical trial of landiolol hydrochloride, in patients with ischemia and post-operative tachycardia, to assess safety and effectiveness of landiolol for control of heart rate (HR) over 11 and 22 minutes of administration.

Trial Design

Tanaka et al. 2008 is a small single-center placebo-controlled double-blind parallel group clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Tanaka et al. 2008 does not report the time frame over which the clinical trial was performed but was performed at a single center in Japan. Similar to Kato et al. 1997, Yoshiya et al. 1997,

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

Yoshiya et al. 2002, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL and supraventricular tachycardia are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Tanaka et al. 2008 enrolled consented patients ≥ 20 years old with SVT that developed within 7 days of surgery. In all cases tachycardia was sustained after correction of known precipitating causes such as hypovolemia and anesthesia. Patients required a HR ≥ 120 bpm and had to be sustained for ≥ 1 minute and 0.1 mV changes in the ST segments on their ECG, in the case of arrhythmia other than sinus rhythm, and sustained for ≥ 3 minutes in the case of sinus tachycardia, as well as complications from either hypertension, myocardial infarction, angina, or ischemic changes on echocardiography. For sinus tachycardia, HR was measured twice at 3 and 1 minute prior to therapy administration.

Patients were excluded if they had a myocardial infarction within 1 month, heart failure with NYHA III or IV, known second or third-degree atrioventricular heart block, or sick sinus syndrome. Patients who were pregnant or lactating, and those that had 'severe' liver, kidney, or blood disorders were also excluded. *There was no exclusion for low blood pressure reported for the trial.*

Patients were prohibited from receiving concomitant antiarrhythmic medications including other beta-adrenergic receptor antagonists, calcium channel antagonists, digitalis, or sympathomimetics. Dopamine and dobutamine could be allowed if the total dose was ≤ 10 mcg/kg/min and the dose was maintained throughout the study. These medication exclusions are reasonable from a clinical standpoint. An antiarrhythmic medication could have been previously used if the time passed since discontinuation of the concomitant medication was ≥ 2 times its half-life.

Tanaka et al. 2008 employed multiple possible dosing regimens for landiolol. Low dose was defined by 30 mcg/kg/min bolus over 1 minute, followed by 10 mcg/kg/min for 10 minutes; moderate dose was defined by 60 mcg/kg/min bolus over 1 minute followed by 20 mcg/kg/min for 10 minutes; high dose was defined by 125 mcg/kg/min bolus over 1 minute followed by 40 mcg/kg/min for 10 minutes. All doses were compared to placebo at paired rates of infusion. Patients were treated with their allocated dosing regimen, but if the targeted bradycardic effect defined by a 20% reduction in HR were not achieved after 11 minutes of administration, the initial dose was discontinued, and the patient was escalated to the next higher defined dosing level. Administration was discontinued if systolic BP dropped by $\geq 20\%$ from baseline or below 90 mmHg, or if diastolic BP dropped below 60 mmHg, or if HR fell below 60 bpm.

ECG and BP monitoring timepoints are not well-established in the publication, and overall, the small sample size and lack of clarity on the administrative and data collection components of the trial impair appropriate interpretation of the published data.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Trial blinding is also not described in the trial publication, nor the randomization scheme or method by which it was carried out.

Reviewer Comment: Overall this small trial with multiple unclear components of trial administration and data collection adds minimal additional supportive evidence in the context of the other submitted clinical trials of landiolol that were included in the submitted application.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome.

For the Tanaka et al. 2008 study, although the primary endpoint is not explicitly stated, it appears to be the proportion of patients who achieve a HR reduction of $\geq 20\%$ as well as a HR < 100 bpm following administration of landiolol or placebo.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. Intention to treat or a treatment policy estimand is reported for the trial results.

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.4.2. Study Results

Compliance with Good Clinical Practices

There is no specific statement on good clinical practice in the published Tanaka et al. 2008 article.

Financial Disclosure

Clinical Review
Mitchell Psocka, MD PhD
NDA 217202
Landiolol hydrochloride

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication. Protocol deviations are not reported. No patients were excluded from the analysis data set.

Table 27. Tanaka et al. 2008 Patient Disposition²³

Analysis Set	Landiolol Low Dose	Landiolol High Dose	Placebo	Total
Randomized	5	3	4	12
Safety analysis set	5	3	4	12
Efficacy endpoint analysis (improvement in HR)	5	3	4	12

Table of Demographic Characteristics

Table 28 shows the distribution of baseline characteristics and the SVT inclusion criteria met for the enrolled patients in Tanaka et al. 2008. Low dosage and high dosage groups refer to landiolol.

²³ 1.11.3 – Clinical Information Amendment
CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

Table 28. Demographic characteristics from Tanaka et al. 2008

	Placebo group 4 cases	Low dosage group 5 cases	High dosage group 3 cases
Age	74.8 ± 8.0	73.2 ± 5.0	63.3 ± 7.8
Weight (kg)	57.9 ± 7.3	53.7 ± 5.3	45.1 ± 7.8
Ratio of male: female	3: 1	3: 2	1: 2
Operative method			
CABG	2	3	1
CABG + AVR	1	1	1
Ascending aortal arch replacement	1	0	0
AVR	0	0	1
AVR + TAP	0	1	0
Arrhythmia			
Sinus tachycardia	1	3	3
Paroxysmal atrial fibrillation	3	2	0
Heart rate before administration (beats/min)	131.0 ± 10.6	133.2 ± 9.3	124.0 ± 2.6

Average ± standard deviation, CABG: Coronary artery bypass graft, AVR: Aortal valve replacement, TAP: Tricuspid annulus plasty

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the included patients was included in the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Tanaka et al. 2008 publication.

Efficacy Results - Primary Endpoint

In Tanaka et al. 2008, a total of 12 patients were enrolled, 4 into the placebo arm, 5 into the low dose group, and 3 into the high dose group. None of the 4 placebo-treated patients achieved a HR decrease of ≥20% with a HR <100 bpm, whereas 4 (80%) patients in the low dose group and 2 (67%) in the high dose group achieved the HR reduction. Overall, thus the number achieving the post-hoc endpoint was 6 (75%) of the 8 landiolol-treated patients. By 11 minutes of administration, the mean HR increased in the placebo group by 2.3%, whereas in the low dose group the mean HR decreased by 26% and the high dose group by 22%.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 29. Summary of landiolol effectiveness in the proposed post-hoc primary endpoint in Tanaka et al. 2008

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Tanaka et al. 2008	75% (n = 8)	0 (n = 4)	Not reported	Not reported	Not applicable. Per-Protocol Set not reported.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Data Quality and Integrity - Reviewers' Assessment

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript. However, no adverse effects of landiolol or placebo treatment were reported in Tanaka et al. 2008, but this could be appropriate ascertainment given the small sample size of the trial.

6.5. Taenaka and Kikawa 2013

6.5.1. Study Design

Overview and Objective

Citation: Taenaka N, Kikawa S. The effectiveness and safety of landiolol hydrochloride, an ultra-short acting b1-blocker, in post-operative patients with supraventricular tachyarrhythmias: a multicenter, randomized, double-blind, placebo-controlled study. Am J Cardiovasc Drugs. 2013a Oct;13(5):353-64.

A randomized placebo-controlled double-blind multi-center parallel group clinical trial of landiolol hydrochloride, in patients with ischemia and post-surgical tachycardia, to assess safety and effectiveness of landiolol for control of heart rate (HR) over 11 or 22 minutes of administration.

Trial Design

Taenaka and Kikawa 2013 is a randomized placebo-controlled double-blind multi-center parallel clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Taenaka and Kikawa 2013 was performed at 38 centers in Japan from 2001 through 2002. Although completed entirely outside of the US, similar to Kato et al. 1997, Yoshiya et al. 1997, and Yoshiya et al. 2002, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL and SVT are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Taenaka and Kikawa 2013 enrolled consented patients ≥ 20 years old prior to scheduled surgery if they had either pre-existing ischemic heart disease defined by prior myocardial infarction or angina requiring treatment, ischemic electrocardiographic or echocardiographic changes, or hypertension requiring antihypertensive treatment. Alternatively, without known cardiovascular disease they could be enrolled if they were undergoing cardiovascular surgery,

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

or resection of esophageal cancer, a thoracotomy, or upper abdominal surgery.

Postoperatively, to proceed in the study, patients needed a post-operative supraventricular tachycardia with HR ≥ 120 bpm sustained for ≥ 3 minutes for patients with sinus tachycardia, or HR ≥ 120 bpm sustained for ≥ 1 minute for patients with SVT or tachycardia that was not sinus rhythm. In all cases tachycardia was sustained after correction of known precipitating causes such as hypovolemia and anesthesia.

Patients were excluded if they had a myocardial infarction within 1 month, 'severe' heart failure with NYHA III or IV, known second or third-degree atrioventricular heart block, or sick sinus syndrome. Patients were also excluded if they had used a beta-adrenergic receptor antagonist within 1 week prior to surgery. Patients who were pregnant or lactating, and those that had liver, kidney, or blood disorders defined by AST ≥ 2.5 -fold normal or 100 IU/L, ALT ≥ 2.5 -fold normal or 100 IU/L, blood urea nitrogen ≥ 25 mg/dL, creatinine ≥ 2 mg/dL, or total bilirubin ≥ 3.0 mg/dL within 2 weeks prior to surgery, were also excluded. *There was no stated exclusion for low blood pressure reported for the trial.*

Patients were prohibited from receiving concomitant antiarrhythmic medications including other beta-adrenergic receptor antagonists, calcium channel antagonists, or sympathomimetics, or cholinesterase inhibitors. If patients had been taking these medications, they had to have been discontinued for at least twice the half-life of the medication. However, if dopamine or dobutamine had been administered by continuous infusion at a dose < 10 mcg/kg/min before administration of the study drug, concomitant administration at the same dose was permitted. Digitalis medicines used before administration of the study drug were also permitted if the pharmacological effect was confirmed to have reached a steady state and the bradycardic effect on the heart rate was constant. These medication exclusions are reasonable from a clinical standpoint.

Taenaka and Kikawa 2013 used weight-based intravenous landiolol hydrochloride dosing, with random allocation to either a low dose or a high dose group, or placebo. In the low dose group, a 30 mcg/kg/min bolus was given over 1 minute followed by 10 mcg/kg/min for 10 minutes, then another bolus of 60 mcg/kg/min over 1 minute was given followed by 20 mcg/kg/min for 10 additional minutes. In the high dose group, a 60 mcg/kg/min bolus was given over 1 minute followed by 20 mcg/kg/min for 10 minutes, then a 125 mcg/kg/min bolus dose was given over 1 minute followed by an additional 10 minutes of 40 mcg/kg/min. The highest dose was the same loading and continuous infusion dose used in Kato et al. 1997 whereas the initial lower dose regimen was used in Yoshiya et al. 2002. Landiolol was reconstituted in normal saline, which was used as the placebo arm infusion.

Patients were continuously monitored during administration of the study drug, but no schedule of assessments was included in the publication.

Dose discontinuation could occur if the targeted HR reduction (≥ 20 % reduction from the

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202

Landirolol hydrochloride

baseline HR and a HR of <100 bpm) was obtained after administration of the initial dose. If the targeted heart-rate reduction was not obtained, a second 1-minute infusion and 10-minute continuous intravenous infusions were given at an increased dose. If the targeted heart rate reduction was obtained during the period of increased-dose administration, administration was completed. If hypotension defined by a systolic BP decrease of $\geq 20\%$ from the baseline SBP and blood pressure $\leq 90/60$ mmHg or marked bradycardia defined by a heart rate of ≤ 60 bpm occurred, administration was discontinued.

Although stated to be “double-blind” neither the techniques used to ensure blinding nor randomization are described in the Taenaka and Kikawa 2013 publication. Although earlier trials have reported that maintaining blinding with a colorless solution diluted in normal saline, the methods to maintain such blinding cannot be presumed to have been employed.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome.

The stated primary endpoint in the Taenaka and Kikawa 2013 publication was the proportion of patients who achieved an improved HR, defined as a $\geq 20\%$ reduction from the baseline HR and a HR of <100 bpm. In this setting, the proposed post-hoc primary endpoint closely matches the primary endpoint of the published clinical trial.

Secondary endpoints included the change in HR, BP, and RPP, as well as ECG parameters.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. Intention to treat or a treatment policy estimand is reported for the trial results.

The Taenaka and Kikawa 2013 publication reports that the primary endpoint was evaluated by the Chi-square test for the proportion of patients who experienced improvement in HR between the treatment groups. The significance level was set at an alpha of 0.025 (two-tailed). Secondary endpoints were analyzed by Dunnett’s multiple comparison and the Chi-square test. Significance was defined as $P \leq 0.05$ (two-tailed).

Protocol Amendments

No protocol amendments to the published trial were reported.

Clinical Review
Mitchell Psocka, MD PhD
NDA 217202
Landiolol hydrochloride

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.5.2. Study Results

Compliance with Good Clinical Practices

“The study was conducted in accordance with the ethical principles of the Helsinki Declaration and Good Clinical Practice.”

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication.

Table 30. Taenaka and Kikawa 2013 Patient Disposition²⁴

Analysis Set	Landiolol Low Dose	Landiolol High Dose	Placebo	Total
Randomized	56	55	54	165
Discontinued after randomization (refer to Table 31 Error! Reference source not found. for reasons for exclusion)	1	4	0	5
Safety analysis set	55	51	54	160
Primary efficacy endpoint analysis (improvement in HR) – Full Analysis Set (FAS)	50	51	50	151
Excluded from Full Analysis Set (FAS) (refer to Table 31)	5	0	4	9

²⁴ 1.11.3 – Clinical Information Amendment

Analysis Set	Landiolol Low Dose	Landiolol High Dose	Placebo	Total
Per-protocol set (PPS)	46	46	46	138
Excluded from Per-protocol set (PPS) (refer to Table 31 for reasons for exclusion)	9	5	8	22

Table 31. Reasons for patient exclusion from Taenaka and Kikawa 2013

Reason for Discontinuation/Exclusion		Landiolol Low Dose	Landiolol High Dose	Placebo	Total
Discontinued after randomization	absence of tachycardia prior to administration of the study drug	1	4	0	5
Excluded from the analysis – Full Analysis Set (FAS)	Protocol deviations and other factors	5	0	4	9
Excluded from the analysis - Per-protocol set (PPS)	Protocol deviations and other factors	9	5	8	22

Protocol Violations/Deviations

Protocol deviations and other factors led to exclusion of 9 patients from the full analysis set and for the exclusion of 22 patients from the per-protocol analysis set, but these are not fully described in the Taenaka and Kikawa 2013 publication.

No patients received intravenous administration of antiarrhythmic agents (propranolol, verapamil, diltiazem, procainamide, disopyramide, mexiletine, lidocaine, aprindine, cibenzoline, or pilsicainide) before or during the study for a period equal to two half-lives of the agent.

Table of Demographic Characteristics

Table 32 shows the shows the distribution of the baseline characteristics for the 151 patients in the full analysis set from the Taenaka and Kikawa 2013 trial. LM= low dose group, in which a 30 mcg/kg/min bolus was given over 1 minute followed by 10 mcg/kg/min for 10 minutes, then another bolus of 60 mcg/kg/min over 1 minute was given followed by 20 mcg/kg/min for 10 additional minutes if patients had not achieved the primary endpoint of HR reduction. MH=

Clinical Review

Mitchell Psocka, MD PhD

NDA 217202

Landirolol hydrochloride

high dose group, in which a 60 mcg/kg/min bolus was given over 1 minute followed by 20 mcg/kg/min for 10 minutes, then a 125 mcg/kg/min bolus dose was given over 1 minute followed by an additional 10 minutes of 40 mcg/kg/min if patients had not achieved the primary endpoint of HR reduction. PP= placebo group. *By Fisher's exact test (Freeman and Halton test); † By Kruskal–Wallis test. There were no substantial demographic differences between the treatment groups. Overall, 62% of the arrhythmias were sinus tachycardia and 34% were AF. The majority of patients were included due to undergoing cardiovascular surgery, or 64%.

Table 32. Demographic characteristics from Taenaka and Kikawa 2013

Background factor	Treatment group			Test result
	PP group	LM group	MH group	
Patients (n)	50	50	51	
Gender [n (%)]				
Male	37 (74.0)	39 (78.0)	36 (70.6)	$p = 0.7153^*$
Female	13 (26.0)	11 (22.0)	15 (29.4)	
Age (years)	64.8 ± 10.5	63.6 ± 11.9	62.2 ± 9.6	$p = 0.2972^\dagger$
Type of supraventricular tachyarrhythmias [n (%)]				
Sinus tachycardia	27 (54.0)	33 (66.0)	34 (66.7)	$p = 0.3631^*$
Paroxysmal atrial fibrillation	23 (46.0)	15 (30.0)	13 (25.5)	
Paroxysmal atrial flutter	0 (0.0)	2 (4.0)	3 (5.9)	
Paroxysmal supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (2.0)	
Site of surgery [n (%)]				
Cardiovascular surgery	32 (64.0)	33 (66.0)	32 (62.7)	$p = 0.7325^*$
Upper abdominal surgery	3 (6.0)	2 (4.0)	0 (0.0)	
Resection of an esophageal cancer	11 (22.0)	12 (24.0)	16 (31.4)	
Thoracotomy	3 (6.0)	3 (6.0)	2 (3.9)	
Total dosage of dopamine/ dobutamine (µg/kg/min)	5.631 ± 4.060	5.123 ± 4.299	4.927 ± 4.690	$p = 0.3697^\dagger$
Baseline heart rate (beats/min)	137.1 ± 14.5	132.8 ± 13.9	131.8 ± 10.2	$p = 0.1642^\dagger$
Baseline SBP (mmHg)	132.7 ± 27.4	127.0 ± 19.6	127.1 ± 24.3	$p = 0.4693^\dagger$
Baseline RPP (bpm · mmHg)	18,196 ± 4,491	16,784 ± 2,570	16,690 ± 3,086	$p = 0.2362^\dagger$

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the included patients was included in the publication.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Taenaka and Kikawa 2013 publication.

Efficacy Results - Primary Endpoint

In Taenaka and Kikawa 2013, a substantially greater proportion of patients achieved the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or an achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently with pooled landiolol treatment than with placebo, Table 33. Unfortunately, the primary endpoint is only reported for 146 of the 151 patients stated to be included in the full analysis set, leaving out 5 additional patients, 2 from the placebo group, 2 from the low-dose group, and 1 from the high dose group. If it is assumed for a sensitivity analysis that all the unreported patients in the placebo group met the primary endpoint, and none in the treated groups, then the pooled proportion of patients that met the primary endpoint would be 2 (4%) of the placebo group and 50 (50%) of the landiolol-treated group.

As a reminder, in the low dose group, a 30 mcg/kg/min bolus was given over 1 minute followed by 10 mcg/kg/min for 10 minutes, then another bolus of 60 mcg/kg/min over 1 minute was given followed by 20 mcg/kg/min for 10 additional minutes if patients had not achieved the primary endpoint of HR reduction. In the high dose group, a 60 mcg/kg/min bolus was given over 1 minute followed by 20 mcg/kg/min for 10 minutes, then a 125 mcg/kg/min bolus dose was given over 1 minute followed by an additional 10 minutes of 40 mcg/kg/min if patients had not achieved the primary endpoint of HR reduction

The treatment effect for the 146 reported patients are broken down in Table 34. 60% of the patients in the low-dose group met the primary endpoint, 42% of patients in the high dose group met the primary endpoint, and no patients in the placebo group met the primary endpoint.

The publication also states that following the first treatment doses in the low-dose and high-dose groups, the percentage of patients that met the primary endpoint were 8% for the low-dose (30 mcg/kg/min over 1 minute then 10 mcg/kg/min for 10 minutes) and 22% for the high dose group (60 mcg/kg/min over 1 minute then 20 mcg/kg/min for 10 minutes). Overall, following the initial dose (at 11 minutes of administration), the percentage change in HR was an increase of $1.5\% \pm 6.8\%$ for placebo, a decrease of $15.0\% \pm 7.4\%$ for the low-dose group, and a decrease of $13.7\% \pm 10.6\%$ for the high-dose group. Following the second dose (at 22 minutes of administration), the percentage change in HR was a decrease of $2.4\% \pm 7.9\%$ for placebo, a decrease of $23.3\% \pm 8.0\%$ for the low-dose group, and a decrease of $18.9\% \pm 10.0\%$ for the high dose group.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

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Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 33. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Taenaka and Kikawa 2013

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Taenaka and Kikawa 2013	51% (n = 98)	0% (n = 48)	Not reported	Not reported	Per-Protocol Set not reported in detail but reported as similar to the Full-Analysis Set.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 34. Decrease in heart rate with landiolol treatment in Taenaka and Kikawa 2013

Treatment group	Improved	Not improved	Improvement rate [% (95 % CI)]	Superiority relative to the PP group ^a	Dose-dependency between LM and MH groups ^b
PP group (<i>N</i> = 48)	0	48	0.0 (0.0–0.0)		
LM group (<i>N</i> = 48)	29	19	60.4 (46.6–74.3)	PP vs. LM <i>p</i> = 0.0001	
MH group (<i>N</i> = 50)	21	29	42.0 (28.3–55.7)	PP vs. MH <i>p</i> = 0.0001	LM vs. MH <i>p</i> = 0.1050

Refer to Table 1 for treatment group definitions

CI confidence interval

^a Chi-square test; significance was defined as *p* < 0.025 (two-tailed) based on Bonferroni correction

^b Chi-square test; significance was defined as *p* < 0.05 (two-tailed)

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

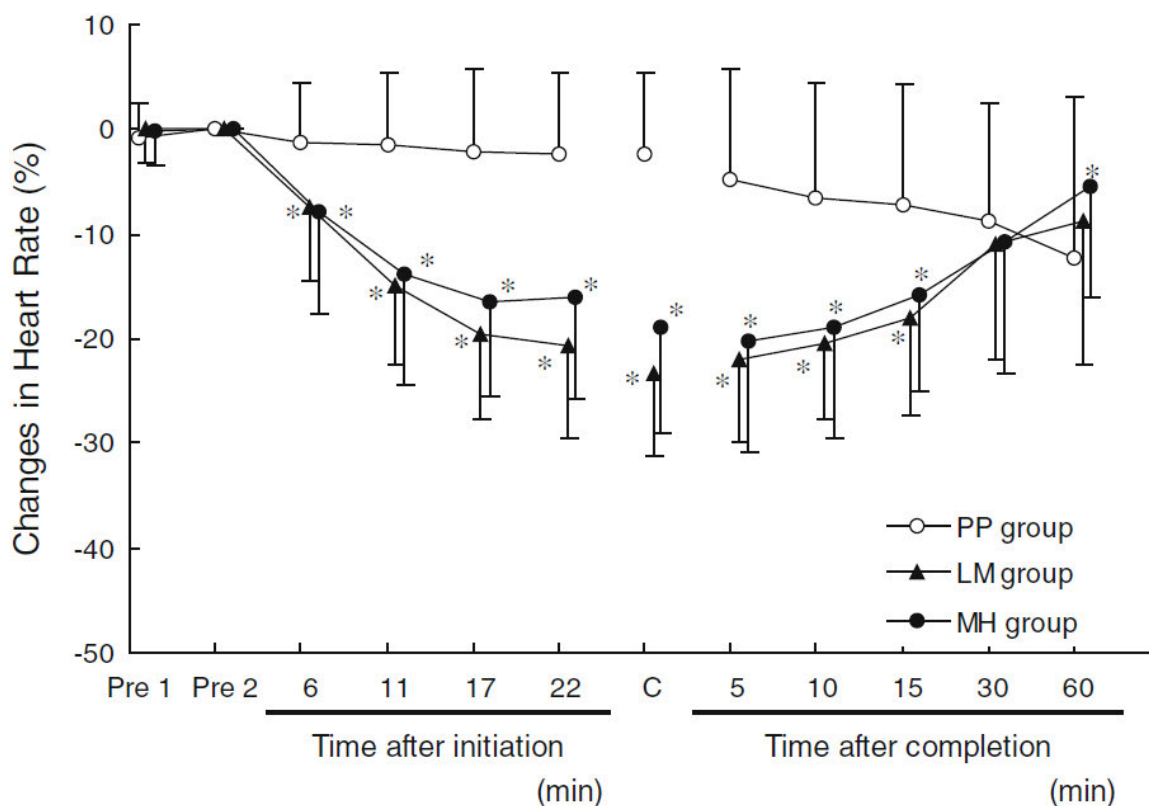
Data Quality and Integrity - Reviewers' Assessment

The loss of 5 patients from the full analysis set without reported outcome data weakens the overall data integrity, even though the sensitivity analysis remains supportive of a treatment effect for landiolol on HR. Otherwise, data quality and integrity could not be further assessed given that the only submission was the published clinical trial manuscript.

Durability and Persistence of Response

Change in HR was captured longitudinally in Taenaka and Kikawa 2013, displayed in Figure 7. The treatment effect of landiolol on HR appeared durable during the 22 minutes of continuous administration, and by 30 minutes after administration had been discontinued the HR in the treated group was similar to placebo. *Dunnett test; significance was defined as $P < 0.05$ (two-tailed). C is the sum of the result immediately after completion of infusion plus the results at discontinuation of infusion.

Figure 7. Durability and persistence of heart rate response in Taenaka and Kikawa 2013



Number of patients

PP group	49	50	50	49	50	48	48	50	50	50	49	48
LM group	50	50	49	49	36	27	48	48	49	50	49	49
MH group	51	51	50	48	36	33	50	50	51	51	51	50

Additional Analyses Conducted on the Individual Trial

Analysis for heterogeneity of treatment effect in prominent subpopulations was undertaken in Taenaka and Kikawa 2013. PP=placebo, LM=low dose landiolol, MH=high dose landiolol; displayed in Table 35. There were no apparent subpopulations for which the treatment effect was heterogenous, including those patients over age 65 years or patients with sinus tachycardia compared to those with other types of SVT.

Table 35. Subpopulation analysis of treatment effect in Taenaka and Kikawa 2013

Stratification factor	Number of patients (improvement rate [%])					
	PP group		LM group		MH group	
	Improved	Total	Improved	Total	Improved	Total
Total	0	48 (0.0)	29	48 (60.4)	21	50 (42.0)
Age (years)						
21–64	0	18 (0.0)	16	23 (69.6)	10	25 (40.0)
65–86	0	30 (0.0)	13	25 (52.0)	11	25 (44.0)
Type of supraventricular tachyarrhythmias						
Sinus tachycardia	0	27 (0.0)	19	32 (59.4)	17	34 (50.0)
Others	0	21 (0.0)	10	16 (62.5)	4	16 (25.0)
Site of surgery						
Cardiac vascular surgery	0	30 (0.0)	21	33 (63.6)	15	32 (46.9)
Resection of an esophageal cancer	0	11 (0.0)	6	10 (60.0)	5	15 (33.3)
Thoracotomy	0	3 (0.0)	1	3 (33.3)	0	2 (0.0)
Amount of dopamine/dobutamine used (µg/kg/min)						
Not used	0	6 (0.0)	2	6 (33.3)	3	10 (30.0)
0.50–5.00	0	21 (0.0)	15	24 (62.5)	8	22 (36.4)
5.01–10.00	0	17 (0.0)	9	14 (64.3)	7	13 (53.8)
10.01–20.00	0	4 (0.0)	3	4 (75.0)	3	5 (60.0)
Baseline heart rate (bpm)						
120–129	0	19 (0.0)	19	25 (76.0)	15	25 (60.0)
130–139	0	10 (0.0)	7	13 (53.8)	3	14 (21.4)
140–189	0	19 (0.0)	3	10 (30.0)	3	11 (27.3)
Baseline systolic blood pressure (mmHg)						
92–139	0	31 (0.0)	19	34 (55.9)	14	35 (40.0)
140–219	0	17 (0.0)	10	14 (71.4)	7	15 (46.7)
Baseline RPP (bpm · mmHg)						
11,280–16,999	0	21 (0.0)	15	26 (57.7)	12	31 (38.7)
17,000–35,916	0	27 (0.0)	14	22 (63.6)	9	19 (47.4)

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

6.6. Sakamoto et al. 2012

6.6.1. Study Design

Overview and Objective

Citation: Sakamoto A, Kitakaze M, Takamoto S, et al. Landiolol, an ultra-short-acting β_1 -blocker, more effectively terminates atrial fibrillation than diltiazem after open heart surgery: prospective, multicenter, randomized, open-label study (JL-KNIGHT study). *Circ J.* 2012;76(5):1097-101.

A randomized active-controlled open-label multi-center parallel clinical trial of intravenous landiolol hydrochloride, in patients with post-operative AF, to assess safety and effectiveness of landiolol for control of HR when compared to intravenous diltiazem.

Trial Design

Sakamoto et al. 2012, also known as the Japan Landiolol kick-off of novel investigation for gold standard heart study (JL-KNIGHT Study), is a randomized active-controlled open-label multi-center, parallel group trial. Compared to the clinical trials described previously in this review, this is an unblinded open-label randomized trial with active control arm utilizing intravenous diltiazem infusion for the management of tachycardia. Diltiazem, as described in Section 2.2, Analysis of Current Treatment Options, is a non-dihydropyridine calcium-channel blocker indicated in the US for the temporary control of rapid ventricular rate in AF or AFL, and for the rapid conversion of paroxysmal SVT to sinus rhythm. Diltiazem is given intravenously as an initial bolus dose of 0.25 mg/kg over 2 minutes then 0.35 mg/kg repeat bolus if needed, then an infusion at 5 mg/hour that can be increased up to 15 mg/h. Thus, comparison with contemporaneous diltiazem is appropriate for the assessment of landiolol safety and effectiveness.

Sakamoto et al. 2012 was performed at 36 centers in Japan from 2008 through 2009. Although completed entirely outside of the US, similar to Kato et al. 1997, Yoshiya et al. 1997, Yoshiya et al. 2002, Tanaka et al. 2008, and Taenaka and Kikawa 2013, the study is felt to be applicable to the US population as paroxysmal post-operative AF is common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Sakamoto et al. 2012 enrolled consented patients between 20 and 85 years old who were undergoing elective cardiothoracic surgery, but prior to surgery. Patients were excluded if they had a myocardial infarction within 3 days prior to enrollment, prior supraventricular arrhythmia that had required treatment, 'severe' heart failure with NYHA III or IV symptoms or left ventricular ejection fraction <35%, known second or third-degree atrioventricular heart block, sick sinus syndrome, or contraindications to beta-adrenergic receptor blockade or calcium

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202

Landirolol hydrochloride

channel blockade. Additional exclusions were known AF with secondary causes such as electrolyte imbalance, Wolff-Parkinson-White syndrome, or hyperthyroidism. Patients with BP <90/60 mmHg were excluded, as well as patients with perioperative antiarrhythmic medication use other than digoxin.

Following enrollment, the patients were randomly assigned to the study drug as delivered by the 'envelope method' and continuously monitored on cardiac telemetry. Further details of the randomization are not adequately described. It is unclear whether details of the randomization process could have affected the clinical trial results.

The study drug was given if postoperative AF or AFL occurred with a ventricular HR $\geq$ 100 bpm for $\geq$ 5 minutes. The diagnostic criteria used for AF or AFL were not described nor whether there was central adjudication of the arrhythmia. Although the diagnostic criteria for AF and AFL are not documented in the submitted trial materials, these are clinically common and have typical non-ambiguous electrocardiographic findings that can be reasonably expected to have been made by the clinical teams treating these patients.

Sakamoto et al. 2012 used weight-based landiolol hydrochloride dosing as a continuous intravenous infusion without bolus initiated at 0.5 mcg/kg/min that could be titrated to 40 mcg/kg/min with changes every 10 minutes as determined to be necessary to achieve a reduction in HR on ECG. The comparator, diltiazem, was administered intravenously as a bolus dose of 0.25 mg/kg over 2 minutes followed by an initial infusion rate of 3 mg/hour that could be titrated up to 15 mg/hour, reassessed at 1-hour intervals. Both landiolol and diltiazem infusions were titrated to achieve the goal HR of <90 bpm for patients in AF. The duration of infusion for both study drugs following onset of AF was 24 hours.

If hypotension, defined as a systolic BP <90 mmHg, or bradycardia, defined as a HR <50 bpm, occurred, the dose of study drug was decreased or discontinued until resolution of hypotension or bradycardia.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq$ 20%, or achieved HR $\leq$ 100 bpm, or that the paroxysm terminated intermittently.

In Sakamoto et al 2012, the stated primary endpoint was the proportion of patients that converted to sinus rhythm from AF after 8 hours of study drug treatment. The secondary endpoints were the proportion of patients that converted to sinus rhythm by 24 hours of treatment, and the proportion of patients who achieved a HR <90 bpm. HR and BP data were collected every hour following initiation of study drug infusion. If AF or AFL was converted

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

to sinus rhythm, the patient was monitored on telemetry for 3 days after the discontinuation of the drug to detect the recurrence of arrhythmia.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. In the context of Sakamoto et al. 2012, there is no stated statistical analysis plan, except to say that “Differences of conversion rates, the percentage of patients achieving rate control, and adverse events were analyzed with Fisher’s exact test or the chi-square test as appropriate. In all analyses, $P < 0.05$ was considered statistically significant.”

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.6.2. Study Results

Compliance with Good Clinical Practices

The Sakamoto et al. 2012 publication includes no statement on compliance with Good Clinical Practice guidelines but does state that the “The study protocol was approved by the institutional review boards and ethics committees of all participating hospitals, and the study was performed in accordance with the Declaration of Helsinki.”

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

The number of potential patients screened for trial enrollment is not included in the publication, however 450 patients were enrolled in the Sakamoto et al. 2012 trial prior to cardiovascular surgery. Of the 420 enrolled patients, 82 developed post-operative AF; no AFL was diagnosed. However, although the Sakamoto et al. 2012 publication states that “82

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202

Landirolol hydrochloride

patients (19.5%) developed postoperative AF and received one of the study drugs,” outcome data are only reported for 71 patients, leaving 11 patients unaccounted for and without endpoint data.

Table 36. Patient disposition in Sakamoto et al. 2012

Analysis Set	Landiolol	Diltiazem	Total
Randomized	210	210	420
Excluded after randomization for missing data or lack of adherence to study protocol	44	41	85
Developed post-operative atrial fibrillation (AF)			82
Safety analysis set	35	36	71
Full-analysis set (FAS)	Not reported	Not reported	82
Excluded from efficacy endpoint analysis for unclear reasons and rationale			11

Protocol Violations/Deviations

Of the 420 enrolled patients in Sakamoto et al. 2012, 85 patients, 44 randomized to landiolol and 41 randomized to diltiazem were excluded due to missing data or lack of adherence to the study protocol. The details of the missing data and nonadherence are not described further, nor whether these patients developed post-operative AF and should be evaluated as part of the effectiveness or safety analyses. Given that the total number of patients who were included and developed AF numbered 82, the excluded patients is a greater number, meaning that if the excluded patients had substantial incidence of AF and were treated, the trial results could not be considered valid or robust. In addition, although 82 patients were diagnosed with post-operative AF, endpoint data are only included for 71, leaving 11 patients that were excluded from analysis for unclear reasons that could have also been due to protocol violations.

Table of Demographic Characteristics

Table 37 shows the distribution of the baseline characteristics of the 71 patients for whom there is endpoint data reported in Sakamoto et al. 2012.

Table 37. Demographic characteristics from Sakamoto et al. 2012

Table 1. Clinical Characteristics: Treated Patients		
	Landiolol (n=35)	Diltiazem (n=36)
Age (years)	70.2±10.6	69.3±8.4
Sex (F/M)	11/24	12/24
Complications		
Hypertension	22	22
Diabetes	10	9
Preoperative oral β -blocker use	6	8
Surgery		
CABG	17	8
VR	10	15
CABG + VR	3	6
Others	5	7
Pre-infusion HR (beats/min)	129±20	131±20
Pre-infusion BP (mmHg)	116±26/62±14	112±17/62±13

Data given as mean ± SD or n.

CABG, coronary artery bypass grafting; VR, valve replacement;
 HR, heart rate; BP, blood pressure.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

No additional baseline information regarding the included patients was included in the publication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Sakamoto et al. 2012 publication.

Efficacy Results - Primary Endpoint

In Sakamoto et al. 2012, a similar proportion of patients achieved HR <90 bpm after 8 hours when treated with landiolol or diltiazem infusions for the 71 patients for whom the endpoint was reported. However, there is substantial missing data at approximately 13% of the patients that were diagnosed with post-operative atrial fibrillation.

Table 38. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Sakamoto et al. 2012

Study Citation	Proportion of Patients Achieving at least Moderate Improvement of Tachycardia at 8 hours (Full-Analysis Set of reported patients)		Proportion of Patients Achieving at least Moderate Improvement of Tachycardia at 8 hours (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Comparator	Landiolol	Comparator	
Sakamoto et al. 2012 [Diltiazem]	54% (n = 35)	31% (n = 36)	Not reported	Not reported	Not applicable. Per-Protocol Set not reported.

Because of the manner in which the data regarding HR reduction are reported in Sakamoto et al. 2012, the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or an achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently, cannot be entirely assessed. Nevertheless, in the 71 patients who have reported endpoint data, there was a similar proportion of patients with HR < 90 bpm or converted to sinus rhythm at 8- and 24-hours following initiation of study drug infusion for patients who received landiolol and those who received diltiazem. Nevertheless, the number of patients who reportedly converted to sinus rhythm and those who did not convert to sinus rhythm but achieved HR control as defined by HR < 90 bpm totaled more than the number of patients in the landiolol treatment group, making the effectiveness data uninterpretable. Therefore, these data are not included in the overall evaluation of effectiveness for landiolol hydrochloride.

Table 39. Conversion to sinus rhythm in Sakamoto et al. 2012

Table 2. Treatment Effects		
	Landiolol (n=35)	Diltiazem (n=36)
Conversion to sinus rhythm		
<8h	19 (54.3)*	11 (30.6)
<16h	21 (60.0)	17 (47.2)
<24h	26 (74.3)	22 (61.1)
HR controlled, but not converted		
<8h	22 (62.9)	18 (50.0)
<24h	29 (82.9)	27 (75.0)
<72h	34 (97.1)*	28 (77.8)
Recurrence of AF	3/26 (11.5)	6/22 (27.2)

Data given as n (%). *P<0.05 vs. diltiazem (χ^2 -test).
 HR, heart rate; AF, atrial fibrillation.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Data Quality and Integrity - Reviewers' Assessment

Data quality and integrity could not be completely assessed given that the only submission was the published clinical trial manuscript, however there was 13% missing data even among the data elements that were reported in the Sakamoto et al. 2012 manuscript. Overall, this level of missing data makes the trial uninterpretable and noncontributory to the assessment of landiolol effectiveness.

Additional Analyses Conducted on the Individual Trial

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

6.7. Nagai et al. 2013

6.7.1. Study Design

Overview and Objective

Citation: Nagai R, Kinugawa K, Inoue H, et al. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultra-short acting β 1-selective blocker landiolol with digoxin (J-Land Study). *Circ J.* 2013;77(4):908-16.

A randomized active-controlled single-blind multi-center parallel clinical trial of intravenous landiolol hydrochloride, in patients with AF or AFL and left ventricular dysfunction, to assess safety and effectiveness of landiolol for control of HR when compared to intravenous digoxin.

Trial Design

Nagai et al. 2013, also known as the J-Land Study, is a randomized active-controlled single-blind multi-center, parallel group trial. Compared to the clinical trials described previously in this review, this is distinct as a single-blind randomized trial with active control arm utilizing intravenous digoxin infusion for the management of tachycardia. Digoxin, as described in Section 2.2, Analysis of Current Treatment Options, is indicated in the US for the control of resting ventricular rate in adults with chronic atrial fibrillation. However, in clinical practice digoxin is used for the management of AF and AFL and is identified in national and international guidelines for this purpose, as also described in Section 2.2, Analysis of Current Treatment Options. Digoxin is administered intravenously as a loading dose of 8-12 mcg/kg in adults, given as 50% initially then 25% every 6-8 hours twice to achieve the total load, then digoxin is given once daily at 2.4-3.6 mcg/kg for maintenance. Therefore, comparison of landiolol with

Clinical Review

Mitchell Psofka, MD PhD

NDA 217202

Landirolol hydrochloride

contemporaneous digoxin is appropriate for the assessment of landiolol safety and effectiveness.

Nagai et al. 2013 was performed at 95 centers in Japan between 2011 and 2012. Although completed entirely outside of the US, the study is felt to be applicable to the US population as the conditions AF and AFL are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

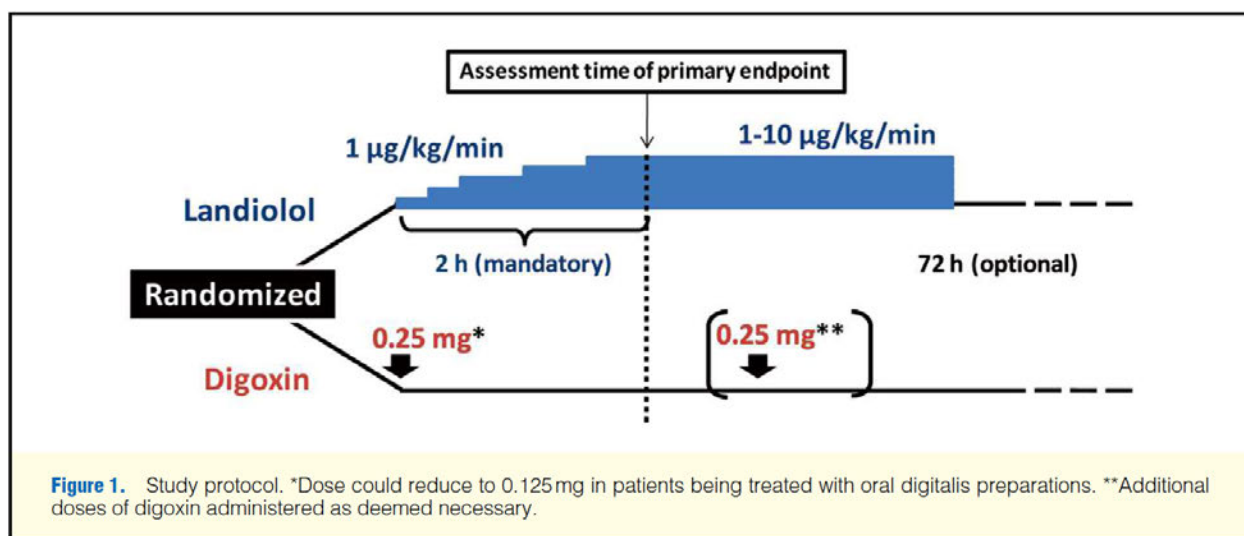
Nagai et al. 2013 enrolled consented patients ≥ 20 years old with heart failure and NYHA III or IV symptoms and a left ventricular ejection fraction of 25-50%, with HR ≥ 120 bpm in AF or AFL.

Patients were excluded if they were deemed to need electrical cardioversion, had 'serious' valvular stenosis, confirmed or suspected hyperthyroidism, an implanted pacemaker or defibrillator, required mechanical ventilation, and if they had systolic BP < 90 mmHg as the definition of cardiogenic shock. Patients were prohibited from receiving concomitant antiarrhythmic medications, calcium channel antagonists, a defibrillator or pacemaker therapies, catheter ablation, until 2 hours after starting treatment, but chronic oral digitalis formulations and beta-adrenergic receptor antagonists were allowed to be continued as prescribed for chronic heart failure treatment. These medication exclusions and inclusions are reasonable from a clinical standpoint.

Nagai et al. 2013 used weight-based landiolol hydrochloride dosing without a bolus. Landiolol hydrochloride was administered intravenously by continuous infusion initiated at 1 mcg/kg/min and increased to a maximum dose of up to 10 mcg/kg/min based on the patient clinical response and HR. Landiolol was administered for at least 2 hours and up to 72 hours. Digoxin was administered at an initial dose of 0.25 mg and could be increased within 72 hours if clinically indicated. If patients were taking chronic digitalis formulations, the load could be reduced to 0.125 mg of intravenous digoxin. As the mean weight of patients in the trial was 60.5 kg, as depicted in Table 41, the dose of 0.25 mg once corresponds to 4.1 mcg/kg initial bolus. This mean initial bolus is appropriate as half the loading dose, but because subsequent completion of the digoxin loading dose was not administered, this dosing of digoxin should be considered incomplete and under-dosed. Therefore, the comparison to the HR slowing effect of digoxin in this study may be a comparison to placebo or no treatment, rather than an effective HR slowing agent. The study schema is depicted in Figure 8.

After completion of the trial observations at 2 hours, landiolol could be transitioned to an oral beta-adrenergic receptor antagonist if deemed appropriate by the treating physician.

Figure 8. Study schema for Nagai et al. 2013



Randomization in Nagai et al. 2013 was by permuted block method. Although the publication states the trial to be ‘single-blind,’ neither the definition of single-blind nor the techniques used to ensure blinding are described in the publication. Although the previously described trials have reported that maintaining blinding with a colorless solution diluted in normal saline, the methods to maintain such blinding cannot be presumed to have been employed.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome.

The Nagai et al. 2013 publication reports a primary endpoint that was the percentage of patients who achieved HR reduction with both a HR < 110 bpm and a $\geq 20\%$ decrease from baseline HR at 2 hours of study drug administration. The secondary endpoints were HR at 0.5, 1, and 2 hours after initiation of the study drug, conversion to sinus rhythm, and subjective patient symptoms at these times. Safety endpoints included the incidence of adverse events.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. Intention to treat or a treatment policy estimand is reported for the trial results.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

The Nagai et al. 2013 publication states: “The primary endpoint was compared between the 2 groups using a linear probability model with HR and LVEF measured immediately before starting the study drug as covariates. The changes in HR and BP after starting the study drugs were compared between the 2 groups using a linear mixed-effects model with adjustment for HR, BP, and left ventricular ejection fraction before starting the study drug. The following covariance structures were considered: unstructured, compound symmetrical, first-order autoregressive, and Toeplitz. The covariance structure that provided the best fit according to the Akaike information criterion was used in the analysis. Assessment times were treated as categorical factors. Student’s t-test was used to compare outcomes between the 2 groups at each time, while the paired t-test was used to compare values between baseline and each time within each group. Bonferroni correction was used for multiple comparisons, except for the change in BP, which was assessed as a safety parameter. Subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) were analyzed using the Wilcoxon rank sum test for comparisons between the 2 groups and the Wilcoxon signed rank sum test for comparisons within each group. Values of $P < 0.05$ were considered statistically significant (2-sided).”

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.7.2. Study Results

Compliance with Good Clinical Practices

There is no statement in Nagai et al. 2013 regarding adherence to Good Clinical Practices, therefore it cannot be assessed.

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

Patient disposition in Nagai et al. 2013, as described in the publication, is included in Table 40. After randomization, 14 patients did not receive the study drug and were excluded from

Clinical Review
Mitchell Psocka, MD PhD
NDA 217202
Landiolol hydrochloride

analysis, though the reasons for their exclusion are not stated. Of the 99 patients who received landiolol, 2 were further excluded due to undescribed protocol deviations. No endpoint data is available for patients who were excluded after randomization prior to receipt of the study drug, thus endpoint data is not available for the full analysis set.

Table 40. Nagai et al. 2013 Patient disposition

Analysis Set	Landiolol	Digoxin	Total
Randomized	99	115	214
Excluded after randomization, study drug not dispensed	6	8	14
Excluded for protocol deviations	2	0	2
Safety analysis set	93	107	200
Per-protocol analysis set	91	107	198

Protocol Violations/Deviations

After randomization, 14 patients did not receive the study drug and were excluded from analysis, though the reasons for their exclusion and whether it was due to protocol deviations, is not stated. Of the 99 patients who received landiolol, 2 were further excluded due to undescribed protocol deviations.

Table of Demographic Characteristics

Table 41 shows the distribution of baseline characteristics for the 200 patients in the safety analysis set from Nagai et al. 2013. Of the SVT, 87% was AF, and the mean left ventricular ejection fraction of the reported patients was $37 \pm 8\%$, and 82% of the patients had NYHA class III heart failure symptoms. Of those patients with reported data, 20% were taking a chronic beta-adrenergic receptor antagonist, and 4% were taking chronic digitalis preparations.

Table 41. Demographic characteristics from Nagai et al. 2013

Table 1. Baseline Characteristics of Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction				
	Total (n=200)	Landiolol (n=93)	Digoxin (n=107)	P value
Demographic characteristics				
Age (years)	71.6±11.5	70.5±12.0	72.5±11.0	0.221
Male, n (%)	106 (53.0)	50 (53.8)	56 (52.3)	0.840
Weight (kg)	60.5±13.2	60.8±13.4	60.2±13.1	0.732
Baseline arrhythmia, n (%)				
Atrial fibrillation	174 (87.0)	80 (86.0)	94 (87.9)	0.095
Atrial flutter	21 (10.5)	8 (8.6)	13 (12.1)	
Atrial fibrillation or flutter	4 (2.0)	4 (4.3)	0 (0)	
Other	1 (0.5)	1 (1.1)	0 (0)	
History of heart failure, n (%)	120 (60.0)	57 (61.3)	63 (58.9)	0.728
Baseline CV disease, n (%)				
Hypertension	133 (66.5)	63 (67.7)	70 (65.4)	0.729
Ischemic heart disease	30 (15.0)	12 (12.9)	18 (16.8)	0.439
DCM	11 (5.5)	6 (6.5)	5 (4.7)	0.582
HCM	2 (1.0)	2 (2.2)	0 (0)	0.127
Hemodynamic parameters				
HR (beats/min)	138.1±15.3	138.2±15.7	138.0±15.0	0.934
SBP (mmHg)	125.7±21.8	124.6±19.8	126.6±23.5	0.523
DBP (mmHg)	84.2±19.2	81.5±16.5	86.5±21.1	0.068
LVEF (%)	36.6±7.6	36.4±7.9	36.7±7.3	0.753
Creatinine (mg/dl)	0.98±0.32	0.98±0.33	0.97±0.32	0.883
BNP (pg/ml)	661.7±561.0	688.0±663.8	639.0±456.6	0.540
NYHA class, n (%)				
III	163 (81.9)	71 (77.2)	92 (86.0)	0.108
IV	36 (18.1)	21 (22.8)	15 (14.0)	
Treatment before administration, n (%)				
Diuretic	100 (50.0)	48 (51.6)	52 (48.6)	0.671
hANP	67 (33.5)	28 (30.1)	39 (36.4)	0.343
β-blocker (oral)	41 (20.5)	18 (19.4)	23 (21.5)	0.708
ARB	31 (15.5)	13 (14.0)	18 (16.8)	0.579
Nitrate	29 (14.5)	11 (11.8)	18 (16.8)	0.317
Aldosterone antagonist	25 (12.5)	11 (11.8)	14 (13.1)	0.789
ACE inhibitor	17 (8.5)	7 (7.5)	10 (9.3)	0.645
Digitalis (oral)	8 (4.0)	6 (6.5)	2 (1.9)	0.099

Data are mean±standard deviation, or n (%).

One patient with PSVT who violated the study protocol was enrolled, but the NYHA class was missing.

ACE, angiotensin-converting enzyme; ARB, angiotensin type 1 receptor blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; hANP, human atrial natriuretic peptide; HCM, hypertrophic cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PSVT, paroxysmal supraventricular tachycardia; SBP, systolic blood pressure.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

No additional baseline information regarding the included patients was included in the publication

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence, non-exclusion concomitant medications, and any explicit rescue medications used are not reported in the Nagai et al. 2013 publication.

Efficacy Results - Primary Endpoint

In the published results of Nagai et al. 2013 a substantially greater proportion of patients achieved a HR reduction of $\geq 20\%$ with a HR < 110 bpm at 2 hours after administration of landiolol compared to placebo, as depicted in Table 42. Although the primary endpoint in the clinical trial was less restrictive with a goal HR of ≤ 110 bpm rather than 100 bpm as included in the proposed post-hoc endpoint, the data regarding the primary endpoint of the trial can be considered to give an estimate of landiolol effectiveness of a magnitude that is likely less than would be seen with a less stringent HR component for the endpoint.

Nevertheless, the endpoint is only reported for 82 of the patients in the landiolol arm and 98 patients in the placebo arm, leaving missing data from those who were administered the study drug for 11 patients (12%) in the landiolol arm, and missing data for 9 patients (8%) in the placebo arm. If all the unaccounted patients treated with digoxin achieved the primary endpoint, and none of the unaccounted patients in the landiolol arm achieved the primary endpoint, then the percentage of patients in the landiolol arm would be 43%, and the percentage of patients who achieved the primary endpoint in the digoxin arm would be 21%, which still supports the presence of a treatment effect on HR. If the same sensitivity analysis is performed on the randomized population prior to exclusion for not receiving the study drug, the percentage of patients who achieved the primary endpoint would be 40% (40 patients out of 99) for the landiolol arm, and 19% (22 patients out of 115) for the digoxin arm.

The percentage of patients who achieved the primary endpoint of a decreased in HR $\geq 20\%$ with a HR < 110 bpm at 2 hours after administration are depicted in Figure 9. Percentage of patients who achieved the primary endpoint by landiolol dose in Nagai et al 2013. The mean dose of landiolol that was required at 2 hours was 6.7 ± 3.2 mcg/kg/min, but there was no evidence of dose dependency, and the effective dose for HR reduction ranged across the tested doses from 1 to 10 mcg/kg/min.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 42. Summary of landiolol effectiveness on the proposed post-hoc primary endpoint in Nagai et al. 2013

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Comparator	Landiolol	Comparator	
Nagai et al. 2013 [Digoxin]	40% (n = 99)	11% (n = 115)	44% (n = 91)	12% (n = 107)	No difference in response rates between Analysis Sets.

Figure 9. Percentage of patients who achieved the primary endpoint by landiolol dose in Nagai et al 2013

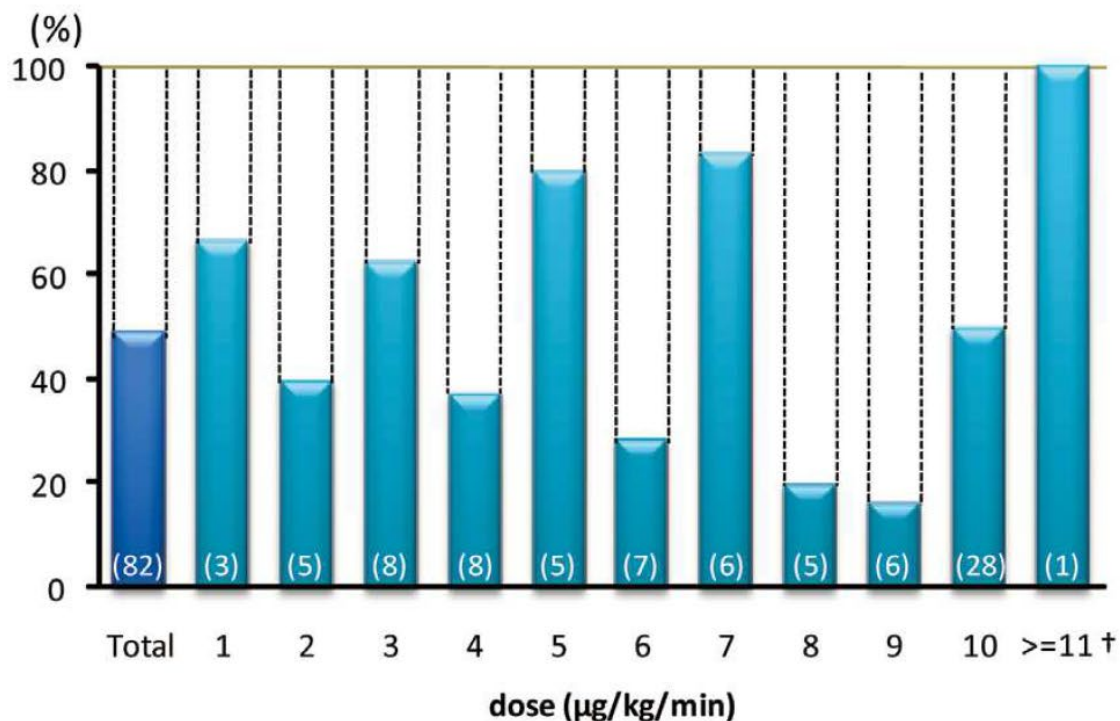


Figure 5. Percentages of patients who achieved the primary endpoint (based on both heart rate <110 beats/min and $\geq 20\%$ decrease in heart rate from baseline at 2h after administration) according to the dose of landiolol (total n=82). †One patient treated at a dose of $15 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ violated the protocol. Data are shown as the percentage of patients in each dose. Values in parentheses are the numbers of patients given each dose.

Data Quality and Integrity - Reviewers' Assessment

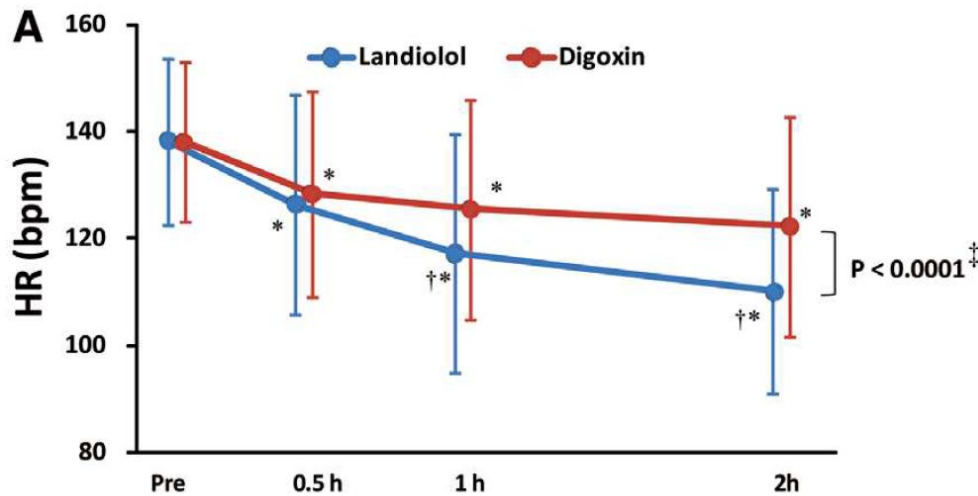
The loss of multiple patients from the full analysis set, including 14 patients who did not receive study drug, and then 2 who received landiolol, weakens the overall integrity of the data. Despite this, the sensitivity analyses are still supportive of the presence of a treatment effect for landiolol on HR in this population. Otherwise, data quality and integrity could not be further assessed given that the only submission was the published clinical trial manuscript.

As described by Figure 9. Percentage of patients who achieved the primary endpoint by landiolol dose in Nagai et al 2013, there was no evidence of dose-dependency to achieve the primary endpoint for the trial, Figure 1. Kato et al. 1997 Schedule of Events

Durability of Response

The HR response for patients who received landiolol or digoxin is graphed in Figure 10. The treatment effect on HR appeared durable over the 2 hours of administration. The decrease in HR from baseline to 2 hours of administration was 27.0 ± 13.3 bpm for landiolol and was 16.0 ± 13.0 bpm for digoxin.

Figure 10. Heart rate response to landiolol and digoxin in Nagai et al. 2013



Patients who received either of the study drugs were followed out to 48 hours initiation of administration, at whatever the final dose that had been needed to attempt to achieve the primary endpoint. These data at 48 hours of administration are shown in Table 43. The decrease in HR appeared durable for landiolol and for digoxin over the 48 hours of extended administration.

Table 43. Patient data at 48 hours of study drug administration in Nagai et al. 2013

Table 3. Changes in Parameters at the Final Observation in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin				
	Landiolol (n=93)		Digoxin (n=107)	
	Pre	Final	Pre	Final
HR (beats/min)	138.2±15.7	98.3±17.6	138.0±15.0	102.3±19.8
SBP (mmHg)	124.6±19.8	113.3±18.4	126.6±23.5	115.5±18.0
DBP (mmHg)	81.5±16.5	72.8±14.3	86.5±21.1	72.1±15.1
LVEF (%)	36.4±7.9	43.1±13.1	36.7±7.3	44.2±11.0
Creatinine (mg/dl)	0.98±0.33	0.99±0.35	0.97±0.32	0.94±0.31
NYHA class, n (%)				
None		0 (0)		1 (0.9)
I		12 (13.6)		12 (11.3)
II		50 (56.8)		51 (48.1)
III	71 (77.2)	24 (27.3)	92 (86.0)	40 (37.7)
IV	21 (22.8)	2 (2.3)	15 (14.0)	2 (1.9)

The final observation was performed at 48 h after the end of administration of landiolol or at 48 h after the final dose in the digoxin group. Abbreviations as in Table 1.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Persistence of Effect

Persistence of treatment effect with landiolol was not evaluated or reported in Nagai et al. 2013.

6.8. Xiao et al, 2014

6.8.1. Study Design

Overview and Objective

Citation: Xiao J, He P, Zou Q, Zhao Y, Xue Z, Deng X, Li S, Guo Q, Tao G, Yang T, Lang Z, He J, Wang X. Landiolol in the treatment of the intraoperative supraventricular tachycardia: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Anesth. 2015 Mar;27(2):120-8.

A randomized placebo-controlled double-blind multi-center parallel group clinical trial of landiolol hydrochloride in patients with intraoperative supraventricular tachycardia, to assess safety and effectiveness of landiolol for control of heart rate over 5 minutes of administration.

Trial Design

Xiao et al., 2014 is a randomized placebo-controlled double-blind multi-center parallel clinical superiority trial. Comparison with contemporaneous placebo is appropriate for the assessment of landiolol safety and effectiveness.

Xiao et al., 2014 was performed at 8 centers in China from 2010 through 2012. Although completed entirely outside of the US, similar to the other randomized controlled trials of landiolol, the study is felt to be applicable to the US population as the conditions paroxysmal AF and AFL and SVT are common in the US population and potential undocumented differences in the populations are believed to be unlikely to affect the mechanism of action nor the safety or effectiveness of the study drug.

Xiao et al., 2014 consented and enrolled patients between 18 and 70 years old prior to scheduled surgery. Patients were identified for possible inclusion in the treatment phase of the study after 30 minutes from the start of the surgery if HR $\geq$ 100 bpm but $\leq$ 150 bpm and lasted for >1 minute if the patient had SVT or >3 minutes if the patient was in sinus rhythm.

Patients were excluded if they had known cause of tachycardia such as hypovolemia, or if they had myocardial infarction within 1 month, 'severe' heart failure with NYHA IV symptoms, known second or third-degree atrioventricular heart block, or sick sinus syndrome, asthma, had

Clinical Review
Mitchell Psocka, MD PhD
NDA 217202

Landirolol hydrochloride

liver, kidney, or blood disorders defined by AST >1.5-fold normal, ALT >1.5-fold normal, or total bilirubin >1.5-fold normal. Patients who were pregnant or lactating were excluded. Other exclusions included body mass index < 18 or >30 kg/m², cardiogenic shock, diabetic ketoacidosis or metabolic acidosis, pulmonary hypertension associated with right ventricular dysfunction, congestive heart failure, pheochromocytoma. *There was no other stated exclusion for low blood pressure reported for the trial.*

Xiao et al., 2014 used weight-based intravenous landiolol hydrochloride dosing with a bolus of 125 mcg/kg over 1 minute followed by 40 mcg/kg/min for 5 to 11 minutes. If the reduction of HR exceeded 10% at 5 minutes, intravenous landiolol at 40 mcg/kg/min was continued for 6 additional minutes. The control group received an intravenous placebo. The rescue medication esmolol could then be used when the reduction of HR did not exceed 10%. Intravenous esmolol was infused with a bolus of 500 mcg/kg over 1 minute then 50 mcg/kg/min for 4 minutes. If the esmolol dose was insufficient for HR reduction, the dose could be increased up to 300 mcg/kg/min for the continuous infusion. HR and BP were recorded before drug injection and 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 minutes after the injection. The ECG was recorded before drug injection and 5, 10, 15, 30, and 60 minutes after the injection.

Study Endpoints

As stated previously, for the purpose of regulatory approval, each submitted clinical trial was analyzed with respect to the proposed post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently. HR is a surrogate outcome. However, although the proportion of patients who achieved HR reduction can be inferred from the proportion of patients who received the rescue medication esmolol, because the use of the rescue medication was not mandatory, the treatment benefit cannot be reliably interpreted from the published data.

The stated primary endpoint in the Xiao et al., 2014 publication was the proportion of patients who received the rescue medication esmolol when the reduction of HR did not exceed 10% after intravenous landiolol for 5 minutes. The proportion who achieved the post-hoc primary endpoint cannot be determined based on reporting of the stated publication primary endpoint.

Secondary end points included HR, BP, and ECG assessments, time to decrease in HR of at least 10%, and time to HR < 100 bpm.

Statistical Analysis Plan

Because the published literature was used exclusively to support effectiveness and safety of landiolol for this application, individual patient-level data was unavailable. Thus, no formal statistical reanalysis on the patient data could be performed. Intention to treat or a treatment policy estimand is reported for the trial results.

CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

122

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

The Xiao et al., 2014 publication reports that the Cochran-Mantel-Haenszel test controlling for differences between centers was used to test differences between the 2 study groups in the binary responses regarding treatment effectiveness.

Protocol Amendments

No protocol amendments to the published trial were reported.

Data Quality and Integrity: Sponsor's Assurance

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

6.8.2. Study Results

Compliance with Good Clinical Practices

Good Clinical Practice is not mentioned in the study publication.

Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current application. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies. The financial disclosures appear adequate.

Patient Disposition

A total of 1224 patients were screened at 8 sites, and 242 patients randomized to placebo or landiolol treatment arms took at least 1 dose of study drug. Patient disposition is expressed in Table 44. Xiao et al. 2014 Patient Disposition.

Table 44. Xiao et al. 2014 Patient Disposition

Analysis Set	Landiolol	Placebo	Total
Randomized	120	122	242
Discontinued after randomization	2	0	2
Safety analysis set	118	122	240
Per Protocol Set	117	122	239
Excluded from Per Protocol Set	1	0	1

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Analysis Set	Landiolol	Placebo	Total
(Protocol deviation)			

Protocol Violations/Deviations

Protocol deviation in 1 patient led to exclusion from the landiolol group, the specific protocol deviation is not mentioned in the publication.

Table of Demographic Characteristics

Table 45 and Table 46 show the distribution of the baseline characteristics for the 240 patients in the full analysis set from the Xiao et al. 2014 trial.

Table 45. Demographic Characteristics from Xiao et al. 2014

Table 1 Demography characteristics in all treated patients

Characteristics	Placebo (n = 122)	Landiolol (n = 118)	P
Sex, no. (%)			
Male	35 (28.69)	36 (30.51)	.7901
Female	87 (71.31)	82 (69.49)	
Age, y			
Mean (SD)	42.48 (11.81)	44.18 (11.46)	.2556
Range (min-max)	20-68	20-69	
Height, cm			
Mean (SD)	161.9 (7.60)	162.8 (6.64)	.3316
Range (min-max)	148-180	143-178	
Weight, kg			
Mean (SD)	58.2 (9.32)	59.2 (9.43)	.3707
Range (min-max)	42-85	42-87	
Body mass index, kg/m ²			
Mean (SD)	22.13 (2.54)	22.28 (2.65)	.6549
Range (min-max)	18.0-29.4	18.0-28.1	
Smoking, no. (%)	15 (12.30)	18 (15.25)	.4623
Alcohol consumption, no. (%)	16 (13.11)	17 (14.41)	.5397
Body temperature, °C			
Mean (SD)	36.58 (0.28)	36.60 (0.32)	.5505
Range (min-max)	36.0-37.3	36.0-37.5	
SBP, mm Hg	120.9 (15.15)	123.3 (13.06)	.1817
Range (min-max)	90-180	92-170	
DBP, mm Hg	75.4 (9.58)	77.2 (9.29)	.1473
Range (min-max)	43-100	53-111	
HR, beats/min			
Mean (SD)	85.3 (12.19)	84.0 (13.08)	.4299
Range (min-max)	60-136.0	62-135	
Respiratory rate, breaths/min			
Mean (SD)	17.8 (2.27)	17.9 (2.29)	.7866
Range (min-max)	12-23	12-25	
Cardiac functional grading, no. (%)			
I	106 (86.89)	102 (86.44)	.9398
II	16 (13.11)	16 (13.45)	
ECG normal, no. (%)	86 (70.49)	82 (68.91)	.4271
PR, s			
Mean (SD)	0.14 (0.02)	0.14 (0.02)	.6840
Range (min-max)	0.06-0.19	0.04-0.21	
QRS, s			
Mean (SD)	0.09 (0.01)	0.09 (0.01)	.5400
Range (min-max)	0.07-0.15	0.06-0.11	
QT, s			
Mean (SD)	0.36 (0.03)	0.36 (0.03)	.9718
Range (min-max)	0.27-0.47	0.28-0.46	

Table 46. Baseline heart rate, blood pressure, electrocardiographics in Xiao et al. 2014

Table 2 Baseline HR, BP, and ECG of all patients with intraoperative supraventricular tachycardia

Characteristics	Placebo (n = 122)	Landiolol (n = 118)	<i>P</i>
HR, beats/min			
Mean (SD)	108.7 (7.67)	108.9 (7.79)	.8648
Range (min-max)	101-137	100-140	
SBP, mm Hg			
Mean (SD)	123.2 (17.99)	120.0 (18.01)	.1715
Range (min-max)	75-175	82-180	
DBP, mm Hg			
Mean (SD)	75.0 (13.72)	72.4 (12.30)	.1211
Range (min-max)	39-133	43-113	
Respiratory rate, breaths/min			
Mean (SD)	12.9 ± 2.71	12.9 ± 2.68	.8907
Range (min-max)	9-20	10-24	
PR, s			
Mean (SD)	0.13 (0.02)	0.13 (0.02)	.5211
Range (min-max)	0.06-0.18	0.06-0.20	
QRS, s			
Mean (SD)	0.08 (0.02)	0.08 (0.02)	.7998
Range (min-max)	0.05-0.13	0.04-0.13	
QT, s			
Mean (SD)	0.35 (0.03)	0.35 (0.03)	.0980
Range (min-max)	0.28-0.42	0.28-0.44	

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment adherence and non-exclusion concomitant medications besides the rescue medication esmolol are not discussed in the Xiao et al. 2014 manuscript.

Efficacy Results - Primary Endpoint

In Xiao et al. 2014, the proportion of patients receiving the rescue medication esmolol was 7.6% (9 of 118) in the landiolol group and 80.3% (98 of 122) in the placebo group. The publication reports the $P < 0.0001$, 95% confidence intervals -81.2% to -64.2%. Mean HR dropped from 110.3 ± 8.6 bpm at baseline in the landiolol group to 86.0 ± 10.4 bpm at 5 minutes after the administration, whereas the placebo group only declined from 110.0 ± 9.6 bpm to 105.1 ± 13.9 bpm after 5 minutes. The trend in HR is shown in Figure 11. Change in Heart Rate in Xiao et al. 2014. The proportion of patients who achieved the post-hoc primary endpoint of either a decrease in HR $\geq 20\%$, or achieved HR ≤ 100 bpm, or that the paroxysm terminated intermittently cannot be determined from the reported data in Xiao et al. 2014 or inferred from the reported primary endpoint in the publication.

Figure 11. Change in Heart Rate in Xiao et al. 2014

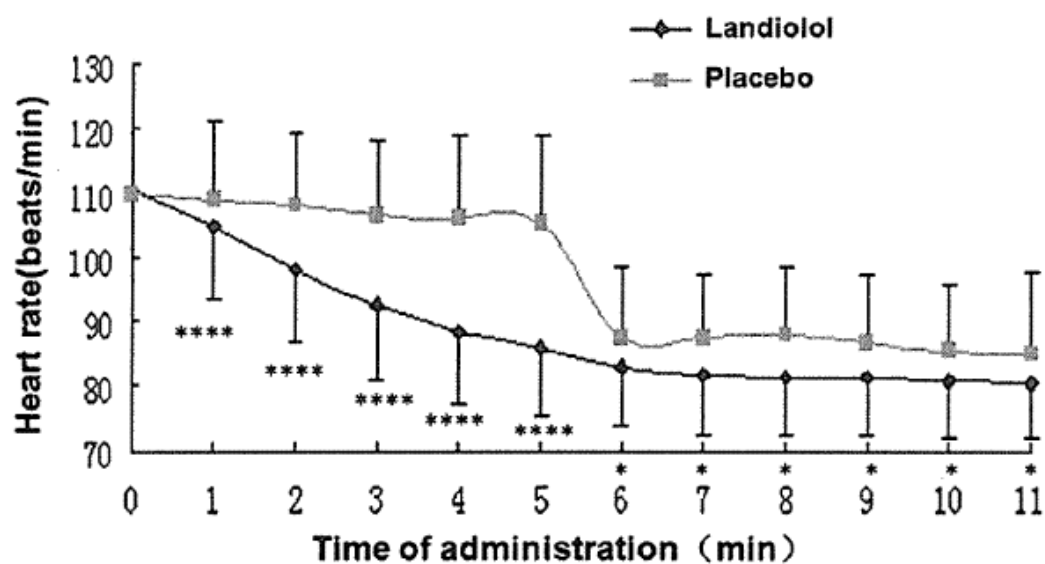


Fig. 2 The reduction of HR after the administration of loading and continuous landiolol or placebo. ****Significant differences vs placebo ($P < .0001$); *Significant differences vs placebo ($P < .05$).

Data Quality and Integrity - Reviewers' Assessment

Data quality and integrity could not be assessed given that the only submission was the published clinical trial manuscript.

Durability and Persistence of Response

Change in HR was captured from 1 to 11 minutes of landiolol administration in Xiao et al. 2014 as depicted in Figure 11. The HR effect of landiolol was persistent up to 11 minutes of administration. Persistence of landiolol effect on HR following landiolol discontinuation were not reported.

Additional Analyses Conducted on the Individual Trial

No additional FDA analyses were undertaken due to the lack of individual patient data, however additional data were presented as part of the publication, including the effect on blood pressure and the adverse event rates. These are presented in Safety Results, section 8.4.

7. Integrated Review of Effectiveness

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride

7.1. **Assessment of Efficacy Across Trials**

APPEARS THIS WAY ON ORIGINAL

7.1.1. Primary Endpoints

Taken together, the 6 randomized placebo-controlled clinical trials and the 2 randomized active-controlled clinical trials support the effectiveness of landiolol to lower HR in the short-term for patients with SVT. Although there is no clear dose-response relationship between dosing and achievement of HR reduction, the tested clinically employed doses appear to be effective when utilized in a monitored setting.

Despite the disparate primary endpoints utilized in each of the randomized controlled trials that support the effectiveness of landiolol for HR reduction, described in Table 3, each trial included as a primary or secondary endpoint the effect of landiolol on HR in the short-term setting. Taken in their totality, these data overall support the assertion that landiolol is able to reduce HR for patients with SVT including those patients with AF and AFL.

Although the details of the blinding processes used remain inadequately described, it is not entirely clear whether details of the blinding process could have affected the trials' results on the physiologic measurement of HR. Thus, it seems likely that there is a true effect of landiolol from the available evidence in spite of the lack of documentation regarding blinding.

Overall, the included trial populations appear similar to patients who might receive landiolol treatment in the US, summarized in Table 47 and Table 48. A wide range of doses were studied in the submitted clinical trials, and although there was no evidence of dose responsiveness, the proposed label employs dosing within the studied range, also summarized in Table 47 and Table 48.

Table 47. Summary demographics for submitted randomized placebo-controlled trials²⁵

Study	Treatment	Infusion dose	N	Gender			Age Mean (standard deviation)	Height Mean (standard deviation)	Weight Mean (standard deviation)
				Male n (%)	Female n (%)	No information available n (%)			
Yoshiya 1997	Landiolol	40 µg/kg/min	136	70 (51.5)	66 (48.5)	0 (0.0)	NA	NA	NA
	Placebo		139	84 (60.4)	55 (39.6)	0 (0.0)	NA	NA	NA
Kato 1997b	Landiolol	80 µg/kg/min	50	29 (58.0)	21 (42.0)	0 (0.0)	60.9 (12.7)	NA	59.5 (9.0)
	Placebo		49	35 (71.4)	14 (28.6)	0 (0.0)	62.8 (9.9)	NA	61.6 (9.9)
Yoshiya 2002	Landiolol	40 µg/kg/min	27	16 (59.3)	11 (40.7)	0 (0.0)	58.3 (13.4)	NA	58.8 (12.7)
	Placebo		27	19 (70.4)	8 (29.6)	0 (0.0)	59.3 (14.6)	NA	59.3 (10.2)
Taenaka and Kikawa 2013a	Landiolol	10 + 20 µg/kg/min	50	39 (78.0)	11 (22.0)	0 (0.0)	63.6 (11.9)	NA	NA
		20 + 40 µg/kg/min	51	36 (70.6)	15 (29.4)	0 (0.0)	62.2 (9.6)	NA	NA
	Placebo		50	37 (74.0)	13 (26.0)	0 (0.0)	64.8 (10.5)	NA	NA
Tanaka 2008	Landiolol	10 + 20 µg/kg/min	5	3 (60.0)	2 (40.0)	0 (0.0)	73.2 (5.0)	NA	53.7 (5.3)
		20 + 40 µg/kg/min	3	1 (33.3)	2 (66.7)	0 (0.0)	63.3 (7.8)	NA	45.1 (7.8)
	Placebo		4	3 (75.0)	1 (25.0)	0 (0.0)	74.8 (8.0)	NA	57.9 (7.3)
Xiao 2015	Landiolol	40 µg/kg/min	118	36 (30.5)	82 (69.5)	0 (0.0)	44.18 (11.46)	162.8 (6.64)	49.2 (9.43)
	Placebo		122	35 (28.7)	87 (71.3)	0 (0.0)	42.48 (11.81)	161.9 (7.60)	58.2 (9.32)

Table 48. Summary demographics for submitted active-controlled trials²⁶

²⁵ Table E1.1: Summary of Demographics for Published Placebo-Controlled Studies

²⁶ Table E1.2: Summary of Demographics for Other Controlled Published Studies

Clinical Review
 Mitchell Pstka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Study	Treatment	Infusion dose	N	Gender			Age Mean (standard deviation)	Height Mean (standard deviation)	Weight Mean (standard deviation)
				Male n (%)	Female n (%)	No information available n (%)			
Nagai 2013	Active		107	56 (52.3)	51 (47.7)	0 (0.0)	72.5 (11.0)	NA	60.2 (13.1)
	Landiolol	1 - 10 µg/kg/min	93	50 (53.8)	43 (46.2)	0 (0.0)	70.5 (12.0)	NA	60.8 (13.4)
Sakamoto 2012	Active		36	24 (66.7)	12 (33.3)	0 (0.0)	69.3 (8.4)	NA	NA
	Landiolol	0.5 - 40 µg/kg/min	35	24 (68.6)	11 (31.4)	0 (0.0)	70.2 (10.6)	NA	NA

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Across the submitted randomized controlled trials, there was evidence of a treatment effect on HR for landiolol, with the magnitude of the treatment effect differing by enrolled population and comparator treatment, as summarized in Table 49 and Table 50. In the setting of inpatient cardiac monitoring, this relatively short-acting medication should be able to be clinically titrated to the desired treatment effect.

Table 49. Summary of landiolol effectiveness on the post-hoc primary endpoint in placebo-controlled trials

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Placebo	Landiolol	Placebo	
Yoshiya et al. 1997	79% (n = 136)	9% (n = 139)	80% (n = 117)	9% (n = 127)	No difference in response rates between Analysis Sets.
Kato et al. 1997	Not reported	Not reported	60% (n = 45)	2% (n = 44)	Not applicable. Full-Analysis Set not reported.
Yoshiya et al. 2002	89% (n = 27)	11% (n = 27)	86% (n = 21)	10% (n = 20)	No difference in response rates between Analysis Sets.
Taenaka and Kikawa 2013	51% (n = 98)	0 (n = 96)	Not reported	Not reported	Per-Protocol Set not reported in detail but reported as similar to the Full-Analysis Set.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Tanaka et al. 2008	75% (n = 8)	0 (n = 4)	Not reported	Not reported	Not applicable. Per-Protocol Set not reported.

Table 50. Summary of landiolol effectiveness on the post-hoc primary endpoint in active-controlled trials

Study Citation	Proportion of Patients Achieving Moderate Improvement of Tachycardia (Full-Analysis Set)		Proportion of Patients Achieving Moderate Improvement of Tachycardia (Per-Protocol Set)		Differences in Response Rates between Analysis Sets as Reported in the Publication
	Landiolol	Comparator	Landiolol	Comparator	
Nagai et al. 2013 [Digoxin]	40% (n = 99)	11% (n = 115)	44% (n = 91)	12% (n = 107)	No difference in response rates between Analysis Sets.

7.1.2. Secondary and Other Endpoints

While tightly linked to the responder analysis primary endpoint of proportion of patients who achieved an at least 20% HR reduction with treatment, the presentation of the continuous HR response data is an alternative endpoint that is supportive of the treatment effect of landiolol on HR. These data are described for each clinical trial by Figure 2. Durability and persistence of heart rate response to landiolol in Kato et al. 1997, Figure 4. Durability and persistence of heart rate response to landiolol in Yoshiya et al. 1997, Figure 6. Durability and persistence of heart rate response in Yoshiya et al. 2002, Figure 7. Durability and persistence of heart rate response in Taenaka and Kikawa 2013, and Figure 10. Heart rate response to landiolol and digoxin in Nagai et al. 2013.

7.1.3. Subpopulations

Due to the lack of individual-patient level data, subgroup analyses of the clinical trial data are not possible, and no relevant subpopulations have been identified. In addition, meta-analyses and complete pooling of the patient data are not possible due to the heterogeneity of the clinical trial populations and intervention dosing. Nevertheless, the consistency across these heterogenous clinical trial populations supports a lack of treatment effect heterogeneity for landiolol among the populations enrolled in these clinical trials. A tabular summary of some of the common critical elements of the baseline populations are displayed in Table 51.

Table 51. Common Baseline Attributes of the Clinical Trial Populations

Trial	Comparator	Age (years)	Sex (% male)	Weight (kg)	SBP (mmHg)	HR (bpm)	% Atrial Fibrillation
Kato 1997 (n=108)	Placebo	61.9 ± 11.4	65%	60.5 ± 9.5	125.4 ± 20.6	117.3 ± 25.8	80% AF 20% AFL

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Trial	Comparator	Age (years)	Sex (% male)	Weight (kg)	SBP (mmHg)	HR (bpm)	% Atrial Fibrillation
Yoshiya 1997 (n=284)	Placebo	60.8	56%	-	139.9	78-105: 40% 106-115: 36% 116-162: 24%	97% Sinus rhythm 3% 'other'
Yoshiya 2002 (n=58)	Placebo	58.3 ± 13.4	65%	58.8 ± 12.7	161.4 ± 26.9	112.1 ± 9.3	89% Sinus rhythm 7% AT
Tanaka 2008 (n=12)	Placebo	71.2	58%	53.0	142.9	130.2	58% Sinus rhythm 42% AT
Taenaka 2013 (n=165)	Placebo	63.5	74%	-	128.9	133.9	62% Sinus rhythm 34% AF
Sakamoto 2012 (n=71)	Diltiazem	70.2 ± 10.6	68%	-	116 ± 26	129 ± 20	100% AF
Nagai 2013 (n=214)	Digoxin (20% on other beta-blockers)	71.6 ± 11.5	53%	60.5 ± 13.2	125.7 ± 21.8	138.1 ± 15.3	87% AF 12% AFL

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

Trial	Comparator	Age (years)	Sex (% male)	Weight (kg)	SBP (mmHg)	HR (bpm)	% Atrial Fibrillation
Xiao 2014 (n=240)	Placebo	44.2 ± 11.5	30%	59.2 ± 9.4	120 ± 18	109 ± 8	Unknown

7.1.4. Dose and Dose-Response

The applicant states: “Given the difference in dosing regimens (in dose and duration and fixed versus titration dose approaches), it is difficult to describe a specific dose-response relationship other than as a range.” In addition, the “overlapping confidence intervals across the 5 placebo-controlled studies do not suggest that within the dose range and dosing regimens evaluated that there is a clear landiolol dose-related effect based on the target primary endpoint.” “Data from uncontrolled studies with more than 1 dose suggest a relatively flat dose response curve and are difficult to interpret without a placebo control and the fixed dose approach.”

On independent review, despite that systemic exposure increases in a dose proportional manner at doses of 10 mcg/kg/min to 80 mcg/kg/min, there is not consistent evidence for a clear dose-response relationship for landiolol and its effect on HR. In the Yoshiya et al. (2000) publication, the proportion of surgical patients with tachycardia and HR ≥ 100 bpm during anesthesia who demonstrated moderate improvement in HR, defined by either intermittent termination of the paroxysm or HR reduction $\geq 20\%$, was 67% with landiolol at 10 mcg/kg/min, 78% at 20 mcg/kg/min, and 91% at 40 mcg/kg/min, which was statistically significant. However, in the Kato et al. (1997) publication, the proportion of patients with atrial fibrillation or atrial flutter and moderate improvement in HR was 56% with landiolol at 20 mcg/kg/min, 62% for 40 mcg/kg/min, and 69% for 80 mcg/kg/min, which was not statistically significant. Of note, the Kato et al. (1997) population was comprised of patients with atrial fibrillation and flutter with mean baseline HR 109-132 bpm and a separate population of patients with paroxysmal SVT and mean baseline HR 164-172 bpm, who were overall less responsive to landiolol treatment and demonstrated no dose response relationship to landiolol. Furthermore, Figure 9. Percentage of patients who achieved the primary endpoint by landiolol dose in Nagai et al 2013, demonstrates no evidence of dose dependency of effect of landiolol, as landiolol was effective for some patients at each of the tested doses from 1 to 10 mcg/kg/min. Therefore, there is no evidence to support dose responsiveness for effectiveness on a population level, and therefore the applicant decision to label only the lower range of tested doses, specifically 10 to 40 mcg/kg/min for patients without heart failure, and 1 to (b) (4) mcg/kg/min for patients with heart failure, is concordant with the available data.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Across the submitted randomized controlled clinical trials, there was consistent rapid onset of action for landiolol with achievement of a reduction in HR by at least 20% in a substantial proportion of the treated population by 5-10 minutes after treatment initiation, as well as a consistent resolution of treatment effect on HR by 30 minutes after landiolol discontinuation. See Figure 2, Figure 4, and Figure 6 for detailed time-dependent graphical representation of the mean response on HR to landiolol administration in the setting of SVT. Over the time courses for which there is detailed follow up data regarding HR after landiolol discontinuation, there does not appear to be a substantial rebound increase in HR effect, but landiolol only appears to be effective for HR reduction while it is being administered.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Effectiveness of landiolol was primarily demonstrated in foreign clinical trials performed outside the United States (US). However, based on the generally accepted effect of beta-1 adrenergic antagonism it is reasonable to presume similar responsiveness to landiolol for patients in the US as patients outside of the US. Although some the clinical trials cited to demonstrate effectiveness of landiolol in the setting of SVT were performed 30 years prior to submission of this application, as reviewed in section 2.2 Analysis of Current Treatment Options, there have not been substantial changes in therapeutic options for these patients since these trials were performed. Finally, while the drug was frequently administered with a bolus dose followed by the infusion, based on the short half-life and onset of action of the drug, use of such a bolus is highly unlikely to have a clinically relevant effect compared to landiolol's use without a bolus on time to HR control.

7.2.2. Other Relevant Benefits

Landiolol appears comparable to esmolol for the short-term reduction in HR for patients with SVT with regards to dosing scheme, rapidity of treatment effect onset, and persistence after discontinuation. There is no data with which to judge relative safety or effectiveness between landiolol and esmolol and therefore these medications cannot be judged to be distinguishable based on the available information. However, at the time of evaluation, esmolol has regulatory approval in the US, as described in Table 1.

7.3. Integrated Assessment of Effectiveness

Based on the sum of the evidence from multiple randomized controlled clinical trials, including 6 placebo-controlled trials, landiolol appears to be effective for reducing HR for patients with SVT including AF and AFL. Although the sponsor-proposed primary effectiveness endpoint is post-hoc, this post-hoc primary endpoint was often a component of the primary endpoint from each of the original published clinical trials, and the effect size appears large. Although the primary endpoint of HR reduction is a surrogate endpoint, this surrogate endpoint was previously agreed upon as an approvable endpoint for a similar agent that received regulatory approval following an advisory committee meeting. Although the clinical trials were performed exclusively outside of the US, principally in Japan, the data are clinically applicable to patients in the US, and it is expected that patients in the US will respond similarly to this specific beta-adrenergic receptor antagonist as they do to other beta-adrenergic receptor antagonists that have supportive data in the US population.

- A statistically and clinically significantly greater proportion of patients with SVT and tachycardia treated with landiolol had decreased HR compared to placebo, according to the proposed post-hoc primary composite endpoint of either a $\geq 20\%$

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

decrease in HR from baseline, decrease in HR to <100 bpm, or conversion to sinus rhythm with treatment. The proportion of patients in each trial with a treatment response and therefore the treatment effects were large and their assessment does not rely on complicated statistical methodologies nor formal meta-analyses (Kato et al. 1997., Yoshiya et al. 1997., Yoshiya et al. 2002., Tanaka et al. 2008., Taenaka and Kikawa 2013., and from the active-controlled trial Nagai et al. 2013). In addition, the Xiao et al, 2014 publication supported effectiveness of a 10% HR reduction after 5 minutes of administration.

- Compared to placebo, between 42% and 89% of patients treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 0-11% of patients did if treated with placebo. For each of the submitted clinical trials, the post-hoc statistical hypothesis test supported a difference in treatment effect between landiolol and the placebo or active comparator. In addition, the hypothesis testing performed as part of the original clinical trials also appeared to support effectiveness of landiolol for HR reduction.
- Although the active controlled trials had substantial loss to follow up, compared to the active controls: 97% of patients treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 78% did with diltiazem treatment; 43% of patients with heart failure treated with landiolol achieved the specified post-hoc primary endpoint of HR reduction, whereas only 12% did with digoxin treatment.
- Although the submitted clinical trial publications utilized heterogeneous populations with non-uniform inclusion and exclusion criteria, variable dosing and titration regimens, and the primary endpoint was post-hoc, the overall effectiveness of landiolol treatment was consistent among the submitted trials and populations.
- The treatment effect for landiolol was consistent for patients with tachycardia and a diagnosis of heart failure with a reduced left ventricular ejection fraction in the Nagai et al. 2013 publication.

• [REDACTED] (b) (4)

- Although there is no evidence of biased publication, specifically clinical trials with landiolol that may have been performed but did not show evidence of a treatment effect on HR that may have been excluded from publication, and although such publication bias cannot be eliminated from possibility, the evidence of a treatment effect for landiolol in the enrolled populations is consistent among the multiple clinical trials performed by multiple investigators at multiple distinct institutions, all unconnected with the current applicant over multiple time periods. Thus, the potential for systematic publication bias that would substantially contradict the published evidence is considered unlikely.

Therefore, the applicant has provided substantial evidence of effectiveness of landiolol for the short-term reduction of heart rate in the intended population of patients with SVT.

The treatment effect, a reduction in HR for patients with SVT with a $\geq 20\%$ decrease in HR from baseline, a decrease in HR to < 100 bpm, or conversion to sinus rhythm, is precisely the treatment effect for which esmolol was previously approved. It was believed by the Cardiovascular and Renal Drugs Advisory Committee meeting on September 29, 1986, that this treatment effect in the inpatient and monitored clinical setting is a clinically meaningful surrogate, as discussed in Section 5.2 Review Strategy. In that Cardiovascular and Renal Drugs Advisory Committee, in which the short-acting beta-1 adrenergic receptor antagonist esmolol was discussed, it was believed that the hypothesis that perioperative HR-slowng would decrease the rate of clinical outcomes was untestable due to the universal application of this hypothesis in routine current clinical practice.²⁷ This hypothesis has remained untested.

There are no comparative effectiveness data comparing landiolol to esmolol for the short-term reduction in HR for patients with SVT with regards to dosing scheme, rapidity of treatment effect onset, and persistence after discontinuation. There are no data with which to judge relative safety or effectiveness between landiolol and esmolol and therefore these medications cannot be judged to be distinguishable based on the available information. While the Sakamoto et al. 2012 clinical trial compared landiolol to intravenous diltiazem for the management of HR, 13% of the data were missing even among the data elements that were reported in the Sakamoto et al. 2012 manuscript. Overall, this level of missing data makes the trial uninterpretable and noncontributory to the assessment of landiolol effectiveness or comparative effectiveness relative to the approved agent diltiazem. There are no other randomized controlled comparative effectiveness data for landiolol with respect to approved available therapies for HR control in the setting of SVT.

8. Review of Safety

8.1. Safety Review Approach

The overall safety review of landiolol relies on the submitted but potentially incompletely ascertained adverse clinical events reported for each randomized controlled clinical trial of landiolol. These data are supplemented by the clinical and regulatory experience with multiple beta-adrenergic receptor antagonists for the purpose of HR control and management of other cardiovascular conditions, including metoprolol and propranolol reported in Table 1. Summary of Pharmacologic Treatments for Supraventricular Tachycardia (SVT). The utilized randomized controlled trials are listed in Table 2. Selected Clinical Trials Relevant to the Landiolol NDA. For the purpose of the safety review, an additional randomized controlled trial contributed data to the safety database that was not included in the primary effectiveness assessment, Xiao et al,

²⁷ https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/19-386_Brevibloc_AdminCorres.pdf

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride
2014.

To formulate estimates of adverse events (AE) with landiolol, safety data for each submitted clinical trial was individually interrogated for the purpose of the safety review. The relevant AEs associated with the drug landiolol were then pooled to create a reasonable estimate of the AE rates for patients treated with landiolol. The primary known safety concern with all of these medications, including those approved for the short-term management of HR in SVT, is hypotension, as described in Table 1. Summary of Pharmacologic Treatments for Supraventricular Tachycardia (SVT). Hypotension, though variably defined, was consistently described as an AE for some patients treated with landiolol and was a focus of the safety assessment for this application. Other AEs known to occur with the class of beta-adrenergic receptor antagonists, including bradycardia, bronchospasm, and heart failure were also specifically interrogated.

The sponsor performed a broader interrogation of the uncontrolled non-randomized published literature that was also assessed for additional otherwise unidentified adverse events. The sponsor identified 41 total studies in which patients were administered landiolol with reported adverse event data, 25 of which were controlled, including the 8 randomized controlled studies included in Table 2. Selected Clinical Trials Relevant to the Landiolol NDA. Overall, 20 of the treatment and prevention trials were placebo-controlled, as depicted in Table 55. Published Placebo-Controlled Treatment and Prevention Population Adverse Events.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database of patients or healthy participants with reported adverse event data from the 8 randomized controlled trials of landiolol included in Table 2. Selected Clinical Trials Relevant to the Landiolol NDA, includes 568 patients with SVT treated with landiolol and 534 patients or participants treated with active control or placebo, described in more detail in Table 52. An additional 45 healthy volunteers received landiolol from the sponsor, and an additional 20 patients with SVT received landiolol from the sponsor in an uncontrolled trial. For the purposes of this review, the safety database is defined by treatment with the study drug, or the as-treated population. The safety database is partially limited by the lack of data reporting for some of the landiolol-treated patients overall, but there is safety data for the majority of patients. The 568 landiolol-treated patients enrolled in randomized controlled trials in the safety database appear to meet the minimum specified in the ICH E1A guideline, even though landiolol is not intended for long-term administration.²⁸

²⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life>

Table 52. Safety Population, Size, and Denominators from Controlled Trials of Landiolol

Safety Database for Landiolol Individuals exposed to any treatment in this development program for the indication under review N=1796 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Landiolol (n=1044)	Active Control (n=143)	Placebo (n=752)
Healthy volunteers	45	-	-
Controlled trials conducted for this indication	568	143	391
All other trials conducted for this indication	20	-	-
Controlled trials conducted for other indications (prevention of SVT)	411	-	361

As the overall individual patient data cannot be pooled for this application, each clinical trial publication was interrogated and analyzed separately for safety. However, both the dosing and the patient populations were heterogenous, which would have also limited the utility of pooling the data if it were possible. All dosing was short-term, most only for 5-22 minutes, with some controlled exposures up to 48 hours, as described in Table 2. Selected Clinical Trials Relevant to the Landiolol NDA. Therefore, the safety of landiolol during administration times greater than these cannot be determined from the currently available data. Of the 568 patients exposed to landiolol in studies for effectiveness for the treatment of SVT, only the 93 patients (16% of the total) in the Nagai et al. 2013 publication were treated for 48 hours, otherwise all patients only received landiolol for 5 to 22 minutes.

Additional randomized controlled trials for the prevention but not treatment of SVT have been performed with landiolol, and these data can also be utilized to help assess the safety of landiolol administration. These include the following clinical trials, referred to by their publications, in Table 53. Description of Prevention-Only Placebo Controlled Studies of Landiolol and Table 54. Description of Prevention-Only Placebo Controlled Studies of Landiolol Continued. These data include at least 411 additional patients exposed to landiolol.

Table 53. Description of Prevention-Only Placebo Controlled Studies of Landiolol²⁹

Study	Treatment	Infusion dose	N	Gender			Age Mean (standard deviation)	Height Mean (standard deviation)	Weight Mean (standard deviation)
				Male n (%)	Female n (%)	No information available n (%)			
Sezai 2011	Landiolol	2 µg/kg/min	70	62 (88.6)	8 (11.4)	0 (0.0)	68.5 (4.7)	NA	NA
	Placebo		70	66 (94.3)	4 (5.7)	0 (0.0)	66.7 (8.9)	NA	NA
Sezai 2012	Landiolol	5 µg/kg/min (LB)	33	26 (78.8)	7 (21.2)	0 (0.0)	68.1 (8.2)	NA	NA
		5 µg/kg/min (L)	34	26 (76.5)	8 (23.5)	0 (0.0)	68.5 (9.6)	NA	NA
	Placebo		34	30 (88.2)	4 (11.8)	0 (0.0)	68.2 (7.5)	NA	NA
Ojima 2017	Landiolol	3 µg/kg/min	50	36 (72.0)	14 (28.0)	0 (0.0)	68	NA	NA
	Placebo		50	41 (82.0)	9 (18.0)	0 (0.0)	69	NA	NA
Suzuki 2014	Landiolol	5 µg/kg/min	21	17 (81.0)	4 (19.0)	0 (0.0)	59.0 (15.6)	163.5 (7.6)	59.4 (12.3)
		2 µg/kg/min	20	17 (85.0)	3 (15.0)	0 (0.0)	65.2 (7.1)	162.0 (7.6)	58.8 (10.6)
	Placebo		20	16 (80.0)	4 (20.0)	0 (0.0)	63.1 (9.8)	162.3 (6.1)	56.9 (11.6)
Yoshida 2017	Landiolol	5 µg/kg/min	39	35 (89.7)	4 (10.3)	0 (0.0)	64	NA	NA
	Placebo		40	32 (80.0)	8 (20.0)	0 (0.0)	62	NA	NA
Kitamura 1997	Landiolol	initial dose: 500 µg/kg	12	7 (58.3)	5 (41.7)	0 (0.0)	43 (16)	NA	NA
		initial dose: 250 µg/kg	10	4 (40.0)	6 (60.0)	0 (0.0)	47 (10)	NA	NA
		initial dose: 100 µg/kg	12	5 (41.7)	7 (58.3)	0 (0.0)	54 (14)	NA	NA
	Placebo		19	8 (42.1)	11 (57.9)	0 (0.0)	45 (16)	NA	NA

²⁹ Sponsor: Table S1.3: Summary of Demographics for Prevention Only Published Placebo-Controlled Studies
 CDER Clinical Review Template
 Version date: September 6, 2017 for all NDAs and BLAs

Table 54. Description of Prevention-Only Placebo Controlled Studies of Landiolol Continued³⁰

Study	Treatment	Infusion dose	N	Gender			Age Mean (standard deviation)	Height Mean (standard deviation)	Weight Mean (standard deviation)
				Male n (%)	Female n (%)	No information available n (%)			
Hasuo 1998	Landiolol	40 µg/kg/min	28	13 (46.4)	15 (53.6)	0 (0.0)	47 (13)	159 (8)	57 (9)
	Placebo		24	12 (50.0)	12 (50.0)	0 (0.0)	41 (10)	159 (9)	56 (12)
Aoki 2020	Landiolol	3 µg/kg/min, 24 h	28	20 (71.4)	8 (28.6)	0 (0.0)	68	NA	NA
	Placebo		28	22 (78.6)	6 (21.4)	0 (0.0)	69	NA	NA
Miyamoto 2021	Landiolol	3 µg/kg/min until cumulative dose of 50 mg reached	23	21 (91.3)	2 (8.7)	0 (0.0)	64 (11)	NA	NA
	Placebo		24	21 (87.5)	3 (12.5)	0 (0.0)	67 (13)	NA	NA
Wajima 2011	Landiolol	40 µg/kg/min	21	0 (0.0)	21 (100.0)	0 (0.0)	42.6 (8.6)	159.5 (5.2)	56.6 (7.1)
	Placebo		21	0 (0.0)	21 (100.0)	0 (0.0)	41.5 (7.9)	158.0 (5.3)	56.0 (7.3)
Horikoshi 2017	Landiolol	5 µg/kg/min	19	15 (78.9)	4 (21.1)	0 (0.0)	67 (7)	160.4 (7.2)	54.7 (7.7)
	Placebo		20	18 (90.0)	2 (10.0)	0 (0.0)	63 (8)	163.9 (6.2)	56 (11.2)
Goyagi 2005	Landiolol	40 µg/kg/min	11	4 (36.4)	7 (63.6)	0 (0.0)	51 (16)	159 (9)	57 (7)
	Placebo		11	5 (45.5)	6 (54.5)	0 (0.0)	55 (18)	162 (12)	62 (13)

³⁰ Sponsor Table S1.3: Summary of Demographics for Prevention Only Published Placebo-Controlled Studies
 CDER Clinical Review Template
 Version date: September 6, 2017 for all NDAs and BLAs

8.2.2. **Relevant characteristics of the safety population:**

All patients studied in the randomized controlled trials of landiolol were located outside of the US, principally in Japan and China, Table 2. From what can be distinguished from the published clinical trials, the safety and effectiveness populations were similar or in some cases identical. As described in the demographics tables from each of the published clinical trials (Table 6. Demographic characteristics of the primary effectiveness analysis from Kato et al. 1997, Table 15. Demographic characteristics of the primary effectiveness analysis from Yoshiya et al. 1997, Table 22. Demographic characteristics from Yoshiya et al. 2002, Table 28. Demographic characteristics from Tanaka et al. 2008, Table 32. Demographic characteristics from Taenaka and Kikawa 2013, Table 37. Demographic characteristics from Sakamoto et al. 2012, Table 41. Demographic characteristics from Nagai et al. 2013, Table 45. Demographic Characteristics from Xiao et al. 2014), and in the summary demographics tables Table 47 and Table 48, as well as in Table 51, the patients given landiolol well-represented both sexes and patient age ranges that are typically affected by SVT including AF and AFL. Because AFL and SVT are common in the US population and in Japan and China, it is presumed that the treatment effect of landiolol would be similar between the non-US and US populations and not vary by racial or location differences. While the BMI of the treated populations likely does not fully encapsulate the current larger BMI range of the US population, it is expected that weight-based dosing with a rapid and monitorable treatment effect should allow safe administration of landiolol.

Landiolol was tested in diverse clinical situations in the clinical trials submitted as evidence, Table 2. Selected Clinical Trials Relevant to the Landiolol NDA. The heterogeneity is a strength of the application, as these clinical situations include the varied clinical contexts in which landiolol is likely to be utilized by treating clinicians. These trials enrolled patients with both non-surgical and perioperative SVT, patients with cardiovascular risk factors, and patients with known cardiovascular disease including symptomatic heart failure. Patients with hepatic dysfunction were systematically excluded from the clinical trials of landiolol, and because there is potential for impact of hepatic dysfunction on the metabolism of landiolol and thereby the determination of appropriate dosing in patients with hepatic dysfunction, landiolol use cannot be deemed safe for those patients with significant hepatic dysfunction.

8.2.3. **Adequacy of the safety database:**

Despite the absence of individual patient safety data that could be used for independent analysis, the total landiolol-exposed population was 568 patients in the 8 randomized clinical trials used for assessment of effectiveness and safety, Table 52. In addition, the absence of additional unexpected adverse events in the approximate (b) (4) patients included in the postmarketing data described in detail in Section 8.9 support the adequacy of the clinical trial safety database. The prevention clinical trial database of landiolol adds at least another 411 patients treated with landiolol at similar doses, summarized in Table 53. Description of Prevention-Only Placebo Controlled Studies of Landiolol and Table 54. Description of Prevention-Only Placebo Controlled Studies of Landiolol Continued, as well as in Table 55.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landirolol hydrochloride
Published Placebo-Controlled Treatment and Prevention Population Adverse Events.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No individual patient data were submitted as part of the applicant data package as all the clinical trial evidence was submitted from the published literature. Therefore, quality of data and adverse event ascertainment could not be rigorously assessed or reanalyzed for each clinical trial. In addition, full study protocols for each clinical trial were unavailable, including the methods of data collection or adverse event evaluation or adjudication. The lack of individual patient data does impair detailed assessment of effectiveness and safety in the context of heterogenous treatment regimens and clinical trial populations, however these issues could not be otherwise addressed by the sponsor due to the inability to recover the primary data used to generate the publications submitted as evidence for effectiveness and safety. Therefore, the application was considered based on the inherent underlying but limited uncertainty present due to the lack of clinical trial protocol and individual patient data submission.

8.3.2. Categorization of Adverse Events

Due to the unavailability of the clinical trial protocols and because the only available data come from the published literature, many of the details regarding AE collection in clinical trials of landiolol remain unknown. None of the landiolol clinical trials explicitly state how AEs were elicited or collected. In addition, no patient narratives were available for review, limiting independent assessment of AEs.

The sponsor collected AE data from all the published placebo-controlled studies for which it was available and coded them according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. These data do not include all patients who received landiolol, as AE data was not available for all patients, but the sponsor included only AEs for those 962 patients in published placebo-controlled trials for whom the AE data were published, tabulated in Table 55. Published Placebo-Controlled Treatment and Prevention Population Adverse Events.

Table 55. Published Placebo-Controlled Treatment and Prevention Population Adverse Events³¹

Study Design	Target (number of studies)	Treatment Groups (number of pts)	Frequency (n and %) of all Adverse Reactions
Placebo Controlled	Treatment and Prevention (n = 20)	Landiolol (962)	157 (16.3%)
		Placebo (799)	126 (15.8%)
	Treatment Only (n = 6)	Landiolol (445)	72 (16.2%)
		Placebo (395)	27 (6.8%)
	Prevention Only (n = 14)	Landiolol (517)	85 (16.4%)
		Placebo (404)	99 (24.5%)

Most publications did not differentiate whether the reported AEs were felt to be related to the study drug, and when not reported it was assumed that the AE was related to the study drug. Due to the lack of individual patient data, but the reporting in the publications of the total number of AEs, the AE reporting assumes that each AE was attributed to a separate patient.

Reviewer Comment: Assuming that each AE is attributed to a single individual for each published trial is a conservative assessment, as typically AEs tend to cluster in fewer individuals, but is appropriate in this case as it aims to prevent underestimation of AE rates in the treated population.

Due to the short duration of landiolol administration in the majority of clinical trials, and the short duration of treatment effect after administration, most AE reporting only includes the time during which patients were administered landiolol and the brief period immediately afterwards, often only 30 minutes to 2 hours.

The safety data are presented as system organ class (SOC) and by preferred term from MedDRA (version 22.1). The sponsor included AEs that occurred in >2 landiolol-treated patients in tabulations of preferred terms. For the purposes of dose responsiveness regarding the AE rate, the sponsor grouped the analyses by dosing groups, with AE assigned to the lowest dose used in that patient population:

³¹ Sponsor 2.7.4 – Sum Clin Safety: Table 11: Summary of Total AEs by Study Design and Target (safety data set)

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

- Very Low dose (LL): Maintenance dose of 1 to <10 mcg/kg/min
- Low dose (L): Maintenance dose of 10 mcg/kg/min
- Medium dose (M): Maintenance dose of 20 mcg/kg/min
- High dose (H): Maintenance dose of 40 mcg/kg/min
- Highest dose (HH): Maintenance dose of 80 mcg/kg/min

8.3.3. Routine Clinical Tests

Laboratory testing in the clinical trials of landiolol suffered from the same liabilities as other data collection: typically, there was no published protocol or timeline of testing, testing was performed only in Japan and China using undescribed laboratory equipment and reference ranges, and in many cases no laboratory testing results are reported in the publications. Nevertheless, laboratory abnormalities were reported as AEs in some the landiolol clinical trials, and narrative descriptions of those treatment trials that included laboratory testing are described below. Of the reported laboratory abnormalities, although the magnitude of changes are not reported, there were no consistent patterns of abnormality and no consistent effect that could be attributable to landiolol treatment. Despite the minimal and inadequately described laboratory testing for patients treated with landiolol, the lack of clinically significant effect on laboratory values is consistent with the mechanism of action and the context of the intended short duration of treatment administration.

In Kato et al. 1997, 1 patient in the landiolol group had a decrease in serum sodium and 1 patient in the placebo group had a decrease in serum sodium. There were no other laboratory abnormalities reported in the landiolol treatment group, described in Table 65.

In Yoshiya et al. 1997, decreased leukocyte count occurred in 1 patient treated with landiolol and no patient treated with placebo. Increased AST and increased ALT occurred in 1 patient each treated with landiolol, and 2 patients treated with placebo had increased AST. One patient had increased total bilirubin in the landiolol-treated and in the placebo groups, 1 patient had a decrease in total cholesterol with landiolol, and 1 patient had a decrease in blood urea nitrogen in the landiolol group. There were no other laboratory abnormalities reported in the landiolol treatment group, described in Table 66.

In Yoshiya et al. 2002, 7 patients in the landiolol group (26%) and 9 patients in the placebo group (33%) experienced a laboratory AE, Table 67. Numerically, for each laboratory abnormality, more patients experienced the change in the placebo arm than the landiolol arm, except for a decrease in platelet count, which occurred in 3 patients treated with landiolol and only 2 patients treated with placebo, and a decrease in total cholesterol, which occurred in 3 patients treated with landiolol and 2 patients treated with placebo.

No laboratory AEs were reported in Taenaka and Kikawa 2013, Sakamoto et al. 2012, Nagai et al. 2013, or Xiao et al. 2014.

8.4. **Safety Results**

8.4.1. **Deaths**

Only one patient was reported to have died in all of the published randomized controlled clinical treatment trials of landiolol. The patient who was reported to have died following treatment with landiolol in Nagai et al. 2013 was a patient who experienced an exacerbation of heart failure that developed 12 hours after completion of the 48-hour administration of landiolol; this same patient died 31 hours after completion of the administration of landiolol. There was also one death in the digoxin arm of Nagai et al. 2013, from sinus arrest. No other deaths were reported in any of the randomized controlled treatment trials. Given the overall short duration of administration, it is not surprising that no deaths occurred during the course of landiolol treatment in these clinical trials. Unfortunately, long-term follow up was not reported for most of the trials, so deaths occurring following short-term administration could not be reliably assessed. Additionally, because only 1 death occurred in the landiolol arms of the treatment clinical trials, the overall risk of landiolol associated mortality is assessed to be low.

8.4.2. **Serious Adverse Events (Hypotension)**

AE rates and serious AE rates between landiolol-treated patients and those who received placebo in the entire safety population including both treatment and prevention trials were similar, with 157 events in the 962 landiolol-treated patients, and 126 in the 799 placebo-treated patients; with assumption of each event representing a distinct patient these data imply a rate of 16.3% for any AE in the landiolol treated population. The major preferred terms were hypotension, hypertension, tachycardia, atrial fibrillation, and abnormal laboratory testing, as delineated in Table 56 for only those adverse events for which there were >2 patients affected. Due to the lack of individual-patient data, it could not be determined whether older patients, or those in other clinical or demographic subgroups were at higher risk of AE when treated with landiolol.

Table 56. Frequency of Adverse Events from Landiolol Placebo-Controlled Clinical Trials

System Organ Class Preferred Term	Treatment Group	
	Landiolol N=962	Placebo N=799
Any adverse event	157 (16.3%)	126 (15.8%)
Vascular disorders	76 (7.9%)	33 (4.1%)
Hypotension	58 (6.1%)	11 (1.4%)
Hypertension	16 (1.7%)	22 (2.8%)
Investigations	27 (2.8%)	20 (2.5%)
Laboratory test abnormal	13 (1.4%)	3 (0.4%)
Cardiac disorders	22 (2.3%)	48 (6.0%)
Tachycardia	11 (1.1%)	20 (2.5%)
Atrial fibrillation	5 (0.5%)	15 (1.9%)

N=number of subjects included in the safety set.

Source: Module 5.3.5.3 [Table S3.1](#)

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

The most common and serious of the adverse events identified associated with landiolol was hypotension, or a clinically significant decrease in BP, which in this accounting occurred in 6.1% of the landiolol-treated patients. In some of the randomized controlled trials hypotension was defined by a BP <90/60 mmHg, in others hypotension was not defined. Hypotension is interpreted to be causally related to landiolol administration given the consistent higher occurrence in landiolol treated patients compared to placebo, the rapid BP reduction that temporally occurs with landiolol administration (Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, Figure 17, Figure 18), the occurrence of hypotension in response to other beta-adrenergic receptor antagonists (Table 1), and the frequent resolution of BP changes with landiolol removal. However, there was no association between the rate of AEs overall or of hypotension with landiolol dose, with doses defined as described in Section 8.3.2, (LL): Maintenance dose of 1 to <10 mcg/kg/min; (L): Maintenance dose of 10 mcg/kg/min; (M): Maintenance dose of 20 mcg/kg/min; (H): Maintenance dose of 40 mcg/kg/min; (HH): Maintenance dose of 80 mcg/kg/min. The dose relationship for landiolol and AEs for those patients in the treatment and prevention placebo-controlled clinical trials is described in Table 57. Frequency of Adverse Events by Landiolol Dose in Treatment and Prevention Placebo-Controlled Trials.

Table 57. Frequency of Adverse Events by Landiolol Dose in Treatment and Prevention Placebo-Controlled Trials

System Organ Class Preferred Term	Treatment/Dose Category						
	Placebo N =799	Landiolol					
		Bolus Only N = 56	LL dose N= 337	L dose N=60	M dose N=54	H dose N=405	HH dose N=50
Any Adverse Reaction	126 (15.8%)	29 (51.8%)	55 (16.3%)	13 (21.7%)	10 (18.5%)	46 (11.4%)	4 (8.0%)
Vascular disorders	33 (4.1%)	25 (44.6%)	1 (0.3%)	6 (10.0%)	5 (9.3%)	36 (8.9%)	3 (6.0%)
Hypotension	11 (1.4%)	13 (23.2%)	1 (0.3%)	6 (10.0%)	5 (9.3%)	32 (7.9%)	1 (2.0%)
Hypertension	22 (2.8%)	12 (21.43%)	0	0	0	3 (0.74%)	1 (2.0%)
Investigations	20 (2.5%)	0	0	7 (11.7%)	6 (11.1%)	13 (3.2%)	1 (2.0%)
Laboratory test abnormal	3 (0.4%)	0	0	7 (11.7%)	6 (11.1%)	0	0
Cardiac disorders	48 (6.0%)	11 (19.6%)	9 (2.7%)	0	0	2 (0.5%)	0
Tachycardia	20 (2.5%)	11 (19.6%)	0	0	0	0	0
Atrial fibrillation	15 (1.9%)	0	5 (1.5%)	0	0	0	0
Nervous system disorders	14 (1.8%)	0	16 (4.8%)	0	0	0	0
Vocal cord paralysis	10 (1.3%)	0	11 (3.3%)	0	0	0	0
Paralysis recurrent laryngeal nerve	3 (0.4%)	0	4 (1.2%)	0	0	0	0
Gastrointestinal disorders	3 (0.4%)	0	6 (1.8%)	0	0	0	0
Gastrointestinal necrosis	0	0	3 (0.9%)	0	0	0	0
Infections and infestations	14 (1.8%)	0	6 (1.8%)	0	0	0	0
Pneumonia	12 (1.5%)	0	5 (1.5%)	0	0	0	0

Source: Module 5.3.5.3 Table S6.1

LL = 1 to <10 µg/kg/min; L = 10 µg/kg/min; M = 20 µg/kg/min; H = 40 µg/kg/min; HH = 80 µg/kg/min

AEs of special interest included those consistent with the mechanism of action of landiolol and known to be associated with other beta-adrenergic receptor antagonists, including hypotension, bradycardia, cardiogenic shock, heart failure, and bronchospasm. The sponsor tabulated these from the treatment and prevention controlled clinical trials in Table 58. The rates of bradycardia, cardiogenic shock, heart failure, and bronchospasm were low and did not suggest an additional substantial effect from landiolol.

Table 58. Adverse Events of Special Interest in Treatment and Prevention Landiolol Clinical Trials

System Organ Class Preferred Term	Treatment Group	
	Landiolol N=962	Placebo N=799
Any adverse event	157 (16.3%)	126 (15.8%)
Hypotension	58 (6.0%)	11 (1.4%)
Bradycardia	2 (0.2%)	1(0.1%)
Shock	1 (0.1%)	0
Cardiac Failure	0	3 (0.4%)
Sinus arrest/ cardiac arrest/ complete AV block	0	0
Bronchospasm	0	0

N=number of subjects included in the safety set.
 Source: Module 5.3.5.3 [Table S4.1](#)

Because of the heterogenous AE descriptions and definitions, sensitivity assessments for hypotension were undertaken. When all events defined as hypotension, either by published report alone or having met a BP reduction cutoff, are used to create an estimate of the rate of hypotension following landiolol administration for tachycardia, the incidence of hypotension with landiolol administration appears higher. The following Table 59. Change in Blood Pressure or Presence of Hypotension in Placebo or Active Controlled Clinical Trials of Landiolol summarizes the available reported data from each of the published submitted active and placebo-controlled clinical trials regarding achievement of a definition of hypotension and the measured decline in BP that occurred with landiolol treatment within the trial. Cumulatively, for those patients with reported data, the rate of hypotension was 11% in the

Landiolol hydrochloride

landiolol-treated patients in these trials compared to <1% following treatment with placebo.

Table 59. Change in Blood Pressure or Presence of Hypotension in Placebo or Active Controlled Clinical Trials of Landiolol

Trial	Change in Systolic Blood Pressure (mmHg)		Symptomatic Hypotension or Blood Pressure <90/50 mmHg in % (n/N)	
	Landiolol	Comparator	Landiolol	Comparator
Kato 1997	-9.0	-4.1	2% (1/50)	0% (0/49)
Yoshiya 1997	-16.0	-5.2	13% (18/136)	<1% (1/139)
Yoshiya 2002	-39.3 ± 35.6	-3.3 ± 18.7	52% (15/29)	34% (10/29)
Tanaka 2008	-11.4 to -12.3	-4.0	0% (0/8)	0% (0/4)
Taenaka & Kikawa 2013	-6.2 to -15.7	-9.7	11% (11/106)	2% (1/54)

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Sakamoto 2012 [Diltiazem]	Not reported	Not reported	11% (4/35)	31% (11/36)
Nagai 2013 [Digoxin]	-10.5	+1.1	8% (7/93)	<1% (1/107)
Xiao 2014	Not reported	Not reported	6% (7/118)	<1% (1/122)
<i>Cumulative</i>	-	-	11% (63/575)	<1% (25/540)

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

In the active-controlled trials the rate of hypotension for landiolol treatment was 11.6% (27/233). If only the hypotensive events occurring temporally associated with study drug (treatment emergent AEs) in the placebo-controlled randomized clinical treatment trials are included in the analysis, as opposed to all the placebo or active-controlled treatment trials, the rate of hypotension is 9.9% (44/445) compared to 1.3% for placebo-treated patients (5/395), Table 60. Adverse Events and Hypotension in Placebo-Controlled Clinical Treatment Trials of Landiolol. The overall AE rate is also higher in these trials than in the overall safety data that include the patients treated in prevention trials, and are likely more representative of the patient population that would receive landiolol treatment in clinical practice. Therefore, these data are believed to be most appropriate for inclusion in the landiolol label (b) (4)

. The absolute difference in AE rates between landiolol treatment and placebo is substantial, approximately 10% of the treated population or a relative risk of 1.9, and almost wholly due to the effect on BP causing hypotension with an absolute risk difference of 8.6% and a relative risk of 7.6 with landiolol treatment.

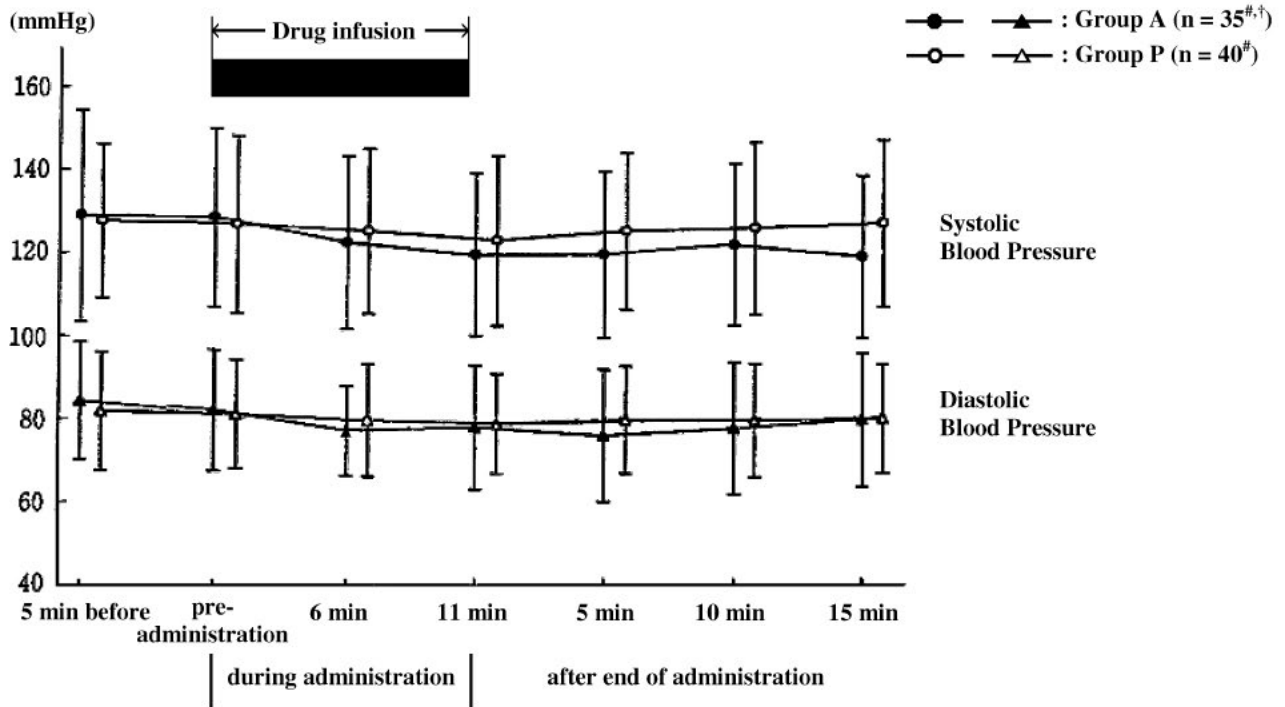
Table 60. Adverse Events and Hypotension in Placebo-Controlled Clinical Treatment Trials of Landiolol

Adverse Reaction	Treatment	
	Landiolol N = 445 n (%)	Placebo N = 395 n (%)
Any adverse reaction	106 (23.8%)	49 (12.4%)
Hypotension	44 (9.9%)	5 (1.3%)

Interrogation of the individual trial BP data demonstrated similar landiolol effects and AE rates. BP safety data for each submitted clinical trial is presented subsequently. Overall, these data demonstrate that the effect of landiolol on BP was consistent among the clinical trial populations and that the temporal change in BP was consistent with the known pharmacokinetics of landiolol (Section 4.5), with onset within 5 minutes of initiation of landiolol administration and resolution of BP effects within 30 minutes in the majority of patients.

In Kato et al. 1997, the mean BP response was relatively mild with regards to change in systolic and diastolic BP over the course of treatment and following the end of administration, shown in Figure 12. A= landiolol and P=placebo. Whereas systolic BP dropped by mean 4 mmHg in the placebo arm after 11 minutes of treatment, it declined by 9 mmHg in the landiolol arm. The mean diastolic BP decline with landiolol at 11 minutes of administration was 4.3 mmHg and it was 2.3 mmHg with placebo.

Figure 12. Blood pressure response to landiolol in Kato et al. 1997

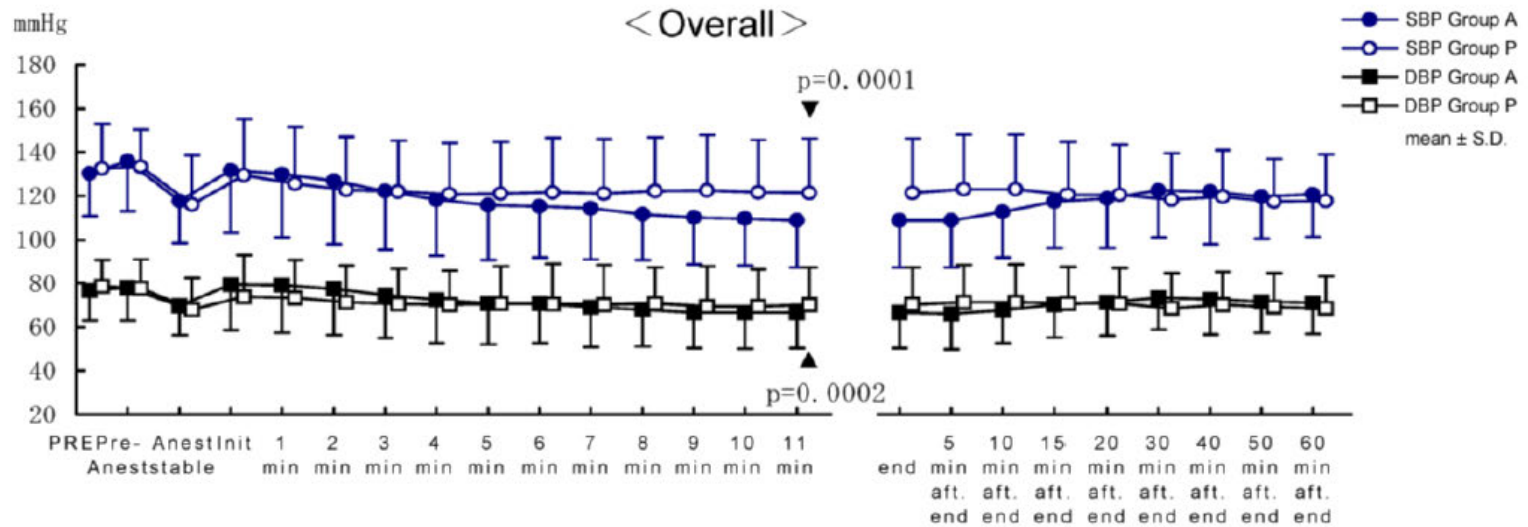


†: 5 min pre-administration values missing for one patient; #: DBP values for one patient completely missing

In Yoshiya et al. 1997, the mean systolic BP response decreased 6.0 mmHg in the landiolol group and 5.2 mmHg in the placebo group after 5 minutes. Mean decrease in diastolic blood pressure was 8.6 mmHg in the landiolol group and 1.7 mmHg in the placebo group after 5 minutes. The time course of blood pressure in patients in whom administration was continued for 11 minutes is shown in Figure 13. A= landiolol and P=placebo. Systolic blood pressure 15 minutes after discontinuation of administration overall was 117.4 ± 21.1 mmHg in the landiolol group and 120.5 ± 24.4 mmHg in the placebo group. Diastolic blood pressure 20 minutes after discontinuation of administration in the overall population was 71.3 ± 15.2 mmHg in the landiolol group and 70.9 ± 16.1 mmHg in the placebo group.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Figure 13. Blood pressure response to landiolol in Yoshiya et al. 1997



patients

SBP	Group A	106	103	107	109	109	109	109	109	109	106	107	109	108	109	109
	Group P	61	62	62	67	67	67	67	67	67	67	67	67	67	67	67
DBP	Group A	106	103	103	109	109	109	109	109	109	106	107	109	108	109	109
	Group P	61	62	62	67	67	67	67	67	67	67	67	67	67	67	67

SBP Group A	109	109	109	109	106	108	104	101	103
SBP Group P	67	67	67	67	67	64	65	63	60
DBP Group A	109	109	109	109	106	108	104	101	103
DBP Group P	67	67	67	67	67	64	65	63	60

Clinical Review

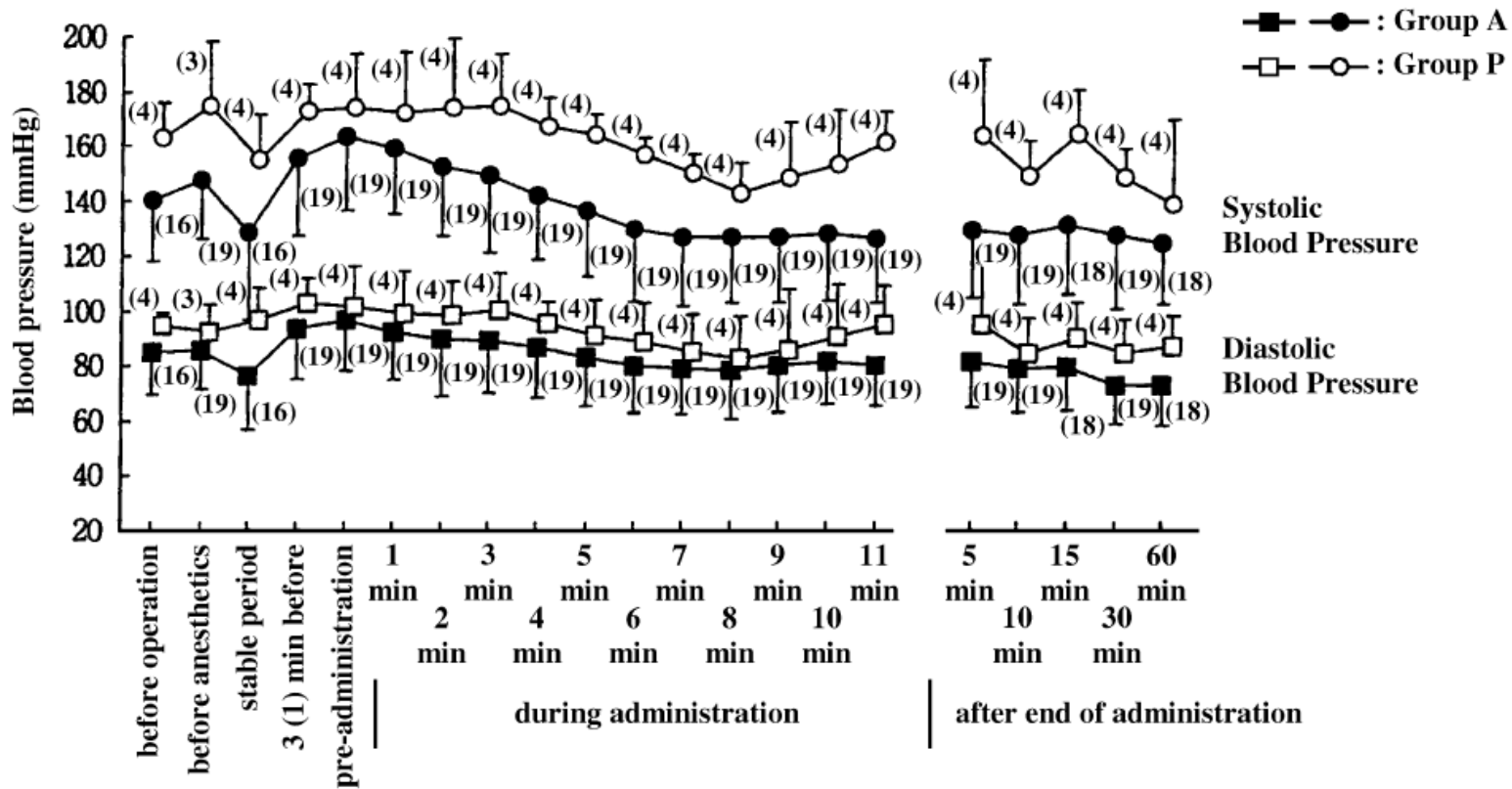
Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

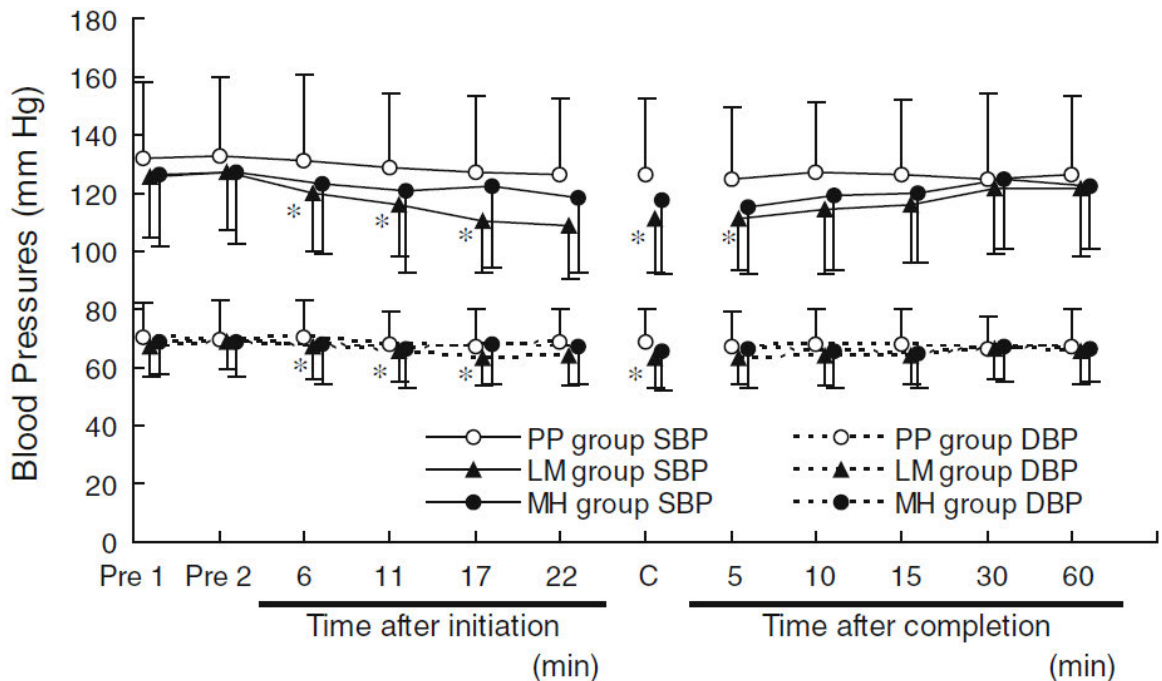
In Yoshiya et al. 2002, after 11 minutes of administration, the mean systolic blood pressure dropped 39.3 ± 35.6 mmHg in the landiolol arm and 3.3 ± 18.7 mmHg in the placebo arm. The mean diastolic blood pressure dropped 18.1 ± 21.2 mmHg in the landiolol arm and 4.0 ± 13.8 mmHg in the placebo arm. These data are graphically represented in Figure 14, A=landiolol and P=placebo.

Figure 14. Blood pressure response in Yoshiya et al. 2002



In Taenaka and Kikawa 2013, after 11 minutes of administration at completion of the first dose in each group, systolic BP decreased in each group. The decrease in systolic BP for placebo was 4.2 ± 12.9 mmHg, the decrease for the low dose was 11.2 ± 11.6 mmHg, and the decrease for the high dose was 5.9 ± 14.1 mmHg. These results for the full analysis data set are displayed in Figure 15. LM= low dose group, in which a 30 mcg/kg/min bolus was given over 1 minute followed by 10 mcg/kg/min for 10 minutes, then another bolus of 60 mcg/kg/min over 1 minute was given followed by 20 mcg/kg/min for 10 additional minutes if patients had not achieved the primary endpoint of HR reduction. MH= high dose group, in which a 60 mcg/kg/min bolus was given over 1 minute followed by 20 mcg/kg/min for 10 minutes, then a 125 mcg/kg/min bolus dose was given over 1 minute followed by an additional 10 minutes of 40 mcg/kg/min if patients had not achieved the primary endpoint of HR reduction. PP= placebo group. *Dunnett test; significance was defined as $P < 0.05$ (two-tailed). At 11 minutes the decrease in diastolic BP was 1.4 ± 6.8 mmHg for placebo, 4.2 ± 5.6 mmHg for the low dose group, and 2.5 ± 6.0 mmHg for the high dose group. After completion of administration at 22 minutes, but including those patients who had their dose discontinued earlier, the decrease in systolic BP was 6.2 ± 18.2 mmHg for placebo, 15.7 ± 14.2 mmHg for low dose, and 9.7 ± 14.7 mmHg for high dose.

Figure 15. Blood pressure response in Taenaka and Kikawa 2013



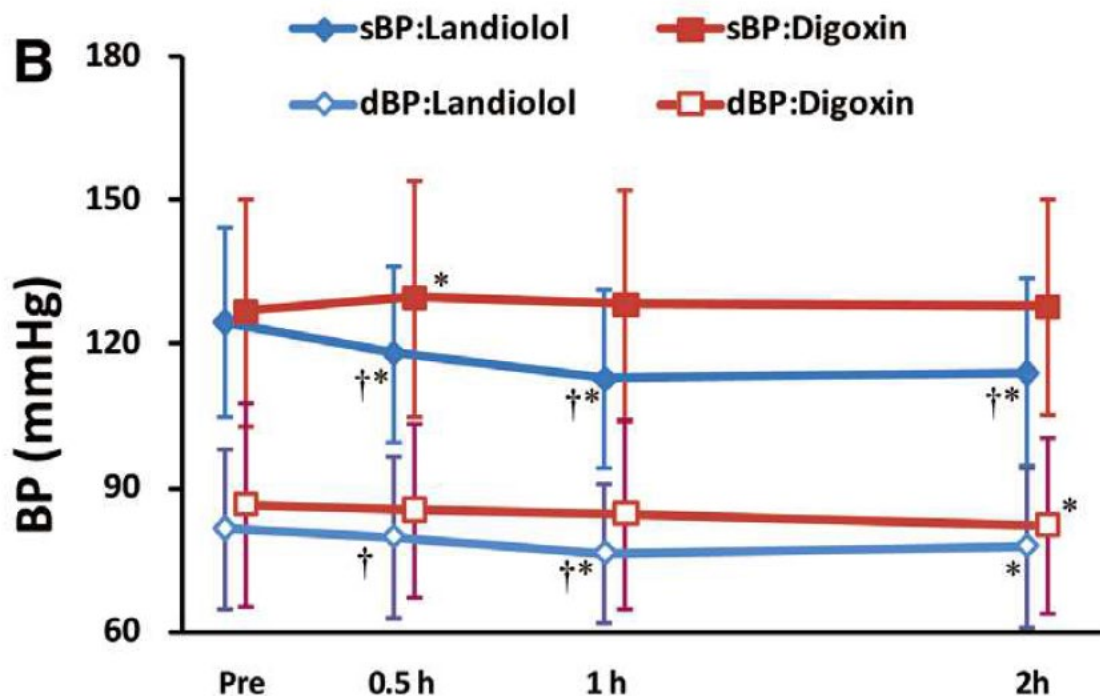
Number of patients

PP group	49	50	50	50	50	49	49	50	50	50	49	48
LM group	50	50	49	49	36	27	48	48	49	50	49	49
MH group	51	51	50	48	36	33	50	51	51	51	51	51

In Nagai et al. 2013, BP decreased following administration of landiolol and of digoxin, as

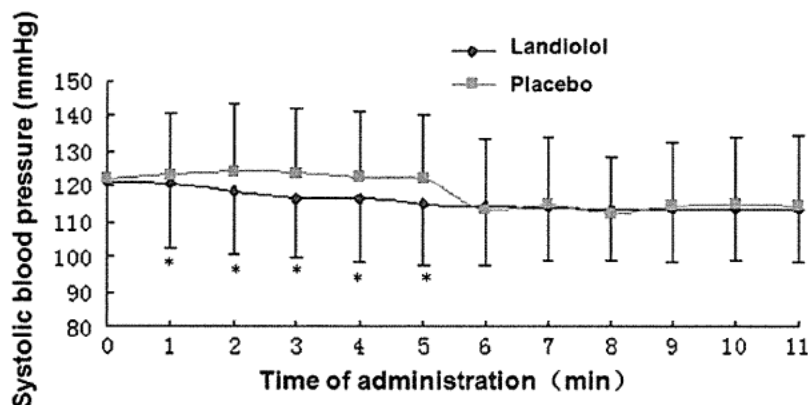
depicted in Figure 16. However, at baseline the mean systolic BP was 125 ± 20 mmHg for landiolol and 127 ± 23 mmHg for digoxin. After 30 minutes of administration, the mean systolic BP for landiolol was 118 mmHg and 129 mmHg for digoxin; after 1 hour the mean systolic BP was 113 mmHg for landiolol and 128 mmHg for digoxin; after 2 hours the mean systolic BP was 114 mmHg for landiolol and 128 mmHg for digoxin. Data are mean $\pm$ standard deviation. ‡Mixed-effects model used to compare data between the landiolol and digoxin groups (interaction: group $\times$ time). † $P < 0.05$ vs. digoxin, * $P < 0.05$ vs. baseline.

Figure 16. Blood pressure following landiolol and digoxin administration in Nagai et al. 2013



In Xiao et al. 2014, the most frequently reported adverse event in those patients treated with landiolol was hypotension, and this was also the most commonly reported adverse event that caused treatment discontinuation. Systolic BP was 121.4 ± 20.2 mmHg in the landiolol group and was 122.2 ± 16.9 mmHg in the placebo group before administration, and at 5 minutes of administration dropped more with landiolol than with placebo, Figure 17. Changes in diastolic blood pressure are reported in Figure 18.

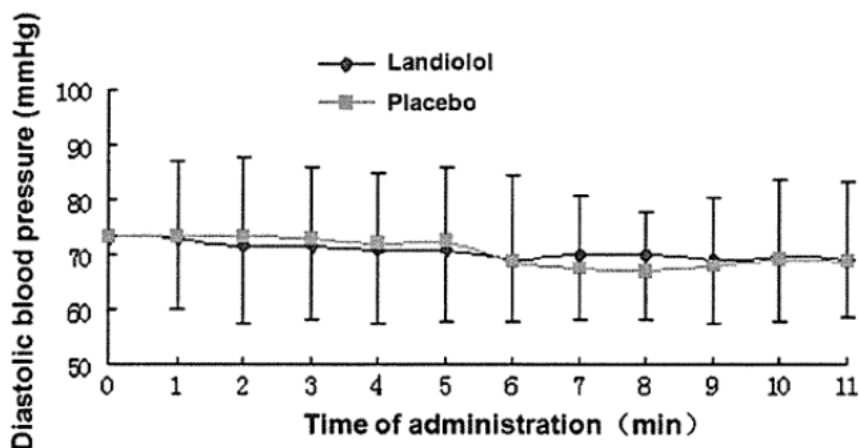
Figure 17. Systolic blood pressure following landiolol administration in Xiao et al. 2014



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The reduction of SBP after the administration of loading and continuous landiolol or placebo. *Significant differences vs placebo (

Figure 18. Diastolic blood pressure following landiolol administration in Xiao et al. 2014



The change of DBP after the administration of loading and continuous landiolol or placebo.

Overall, the changes in BP in response to landiolol were consistent among the clinical trials and associated with a predictable, monitorable, but also consistent rate of clinical hypotension.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Due to the short duration of administration of landiolol in the majority of the randomized controlled trials for treatment of SVT, typically ranging from 5 to 22 minutes, there were few discontinuations of treatment reported. In total, from the randomized controlled treatment trials for SVT, 13 patients treated with landiolol had administration discontinued due to AEs, of the total 568 patients treated with landiolol (2.3%). The majority of these events were aligned with the reported clinical trial protocols in that the administration of landiolol was discontinued

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

for a pre-specified AE, typically hypotension. Patients did not appear to drop out of the clinical trials due to these AE events or landiolol discontinuation and their data was able to be included in the safety and effectiveness analyses. Nonetheless, the patient disposition remains unclear for those treated in Sakamoto et al. 2012, as described in Section 6.6.2 and Table 36. Due to these issues, the Sakamoto et al. 2012 clinical trial was excluded from the safety and effectiveness analyses.

Narrative reviews of the landiolol discontinuations are as follows:

In Yoshiya et al. 1997, 2 patients out of 136 treated with landiolol, or 1.5%, discontinued treatment due to AEs. In both cases the AE event was hypotension that occurred at 5 minutes or 6 minutes of administration.

In Yoshiya et al. 2002, 1 patient had landiolol discontinued after 1 minute of administration due to ECG change in ST-segment from -0.05 mV to -0.10 mV with a RPP of 16,909 bpm x mmHg, which was clinically determined to be an excessive hemodynamic workload, but no further data is reported regarding this patient. Another single patient had landiolol infusion discontinued due to hypotension, which reportedly resolved after subsequent discontinuation of the concomitant inhaled anesthetic. Landiolol was able to be continued in the other patients who developed hypotension in Yoshiya et al. 2002.

In Taenaka and Kikawa 2013, 5 patients with AEs of hypotension with landiolol administration had landiolol discontinued leading to resolution of the hypotension.

In the Nagai et al. 2013 trial, where patients would be treated up to 24 hours, there were AE-associated discontinuation events reported, and the only AEs that led to study drug discontinuation in the landiolol arm occurred within the first 2 hours of treatment, Table 70. The rate of landiolol discontinuation in this setting was 3% or 3 of 93 patients that received landiolol in the first 2 hours of administration. The 3 patients who had landiolol discontinued due to AE had 1 each of an embolic stroke, hypotension, and asthma exacerbation.

In Xiao et al. 2014, patients were switched from landiolol to esmolol for ineffectiveness on HR reduction, but these landiolol discontinuations were not due to AE occurrence. See Section 6.8.2 for details. A single patient discontinuation due to AE was reported in the Xiao et al. 2014 clinical trial, but the etiology of the AE is not reported.

8.4.4. Significant Adverse Events

The sponsor-provided tabulation of MedDRA preferred term AEs taken from all published placebo-controlled studies for SVT treatment are included in

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Table 61, Table 63, and Table 63. These include data from 445 patients treated with landiolol and from 395 patients treated with placebo. Almost the entirety of the absolute difference in

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

overall AE rates between the patients treated with landiolol and those treated with placebo can be attributed to the development of hypotension in a greater proportion of those patients treated with landiolol, 9.9% compared to 1.3% for placebo. As described in Section 8.4.2, hypotension is therefore the predominant significant, severe, and treatment emergent AE associated with landiolol administration. In addition.

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Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 61. Adverse Event Frequency for Placebo-Controlled Treatment Trials³²

System organ class	Preferred term	Landiolol	Placebo
Number of subjects		445 (100.00%)	395 (100.00%)
Total with adverse events	Patients with AE	72 (16.18%)	27 (6.84%)
Vascular disorder	Total	49 (11.01%)	6 (1.52%)
	Hypotension	44 (9.89%)	5 (1.27%)
	Hypertension	3 (0.67%)	1 (0.25%)
	Hot flush	1 (0.22%)	0 (0.00%)
	Shock	1 (0.22%)	0 (0.00%)

³² Sponsor: Table S3.2: Summary of the Frequency of All Adverse Events by SOC and Preferred Term for Treatment Only Published Placebo-Controlled Studies

Table 62. Adverse Event Frequency for Placebo-Controlled Treatment Trials Continued³³

System organ class	Preferred term	Landiolol	Placebo
Investigations	Total	27 (6.07%)	20 (5.06%)
	Laboratory test abnormal	13 (2.92%)	3 (0.76%)
	Alanine aminotransferase increased	2 (0.45%)	1 (0.25%)
	Aspartate aminotransferase increased	2 (0.45%)	3 (0.76%)
	Electrocardiogram ST segment depression	2 (0.45%)	0 (0.00%)
	Blood bilirubin increased	1 (0.22%)	4 (1.01%)
	Blood cholesterol decreased	1 (0.22%)	0 (0.00%)
	Blood sodium decreased	1 (0.22%)	1 (0.25%)
	Blood urea decreased	1 (0.22%)	0 (0.00%)
	Electrocardiogram T wave inversion	1 (0.22%)	1 (0.25%)
	Platelet count decreased	1 (0.22%)	1 (0.25%)
	Pulmonary arterial pressure increased	1 (0.22%)	0 (0.00%)
	White blood cell count increased	1 (0.22%)	2 (0.51%)
	Blood creatine phosphokinase increased	0 (0.00%)	1 (0.25%)
	Blood lactate dehydrogenase increased	0 (0.00%)	1 (0.25%)
	Blood uric acid decreased	0 (0.00%)	1 (0.25%)
	Haematocrit decreased	0 (0.00%)	2 (0.51%)
	Haemoglobin decreased	0 (0.00%)	2 (0.51%)
	Protein total decreased	0 (0.00%)	1 (0.25%)
	Protein urine present	0 (0.00%)	1 (0.25%)

³³ Sponsor: Table S3.2: Summary of the Frequency of All Adverse Events by SOC and Preferred Term for Treatment Only Published Placebo-Controlled Studies

Table 63. Adverse Event Frequency for Placebo-Controlled Treatment Trials Continued³⁴

System organ class	Preferred term	Landiolol	Placebo
	Red blood cell count decreased	0 (0.00%)	2 (0.51%)
Cardiac disorders	Total	2 (0.45%)	3 (0.76%)
	Bradycardia	2 (0.45%)	0 (0.00%)
	Extrasystoles	0 (0.00%)	1 (0.25%)
	Ventricular extrasystoles	0 (0.00%)	2 (0.51%)
General disorders and administration site conditions	Total	2 (0.45%)	0 (0.00%)
	Chills	1 (0.22%)	0 (0.00%)
	Pyrexia	1 (0.22%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders	Total	1 (0.22%)	0 (0.00%)
	Respiratory disorder	1 (0.22%)	0 (0.00%)
Skin and subcutaneous tissue disorders	Total	1 (0.22%)	0 (0.00%)
	Erythema	1 (0.22%)	0 (0.00%)
Gastrointestinal disorders	Total	0 (0.00%)	1 (0.25%)
	Vomiting	0 (0.00%)	1 (0.25%)

³⁴ Sponsor: Table S3.2: Summary of the Frequency of All Adverse Events by SOC and Preferred Term for Treatment Only Published Placebo-Controlled Studies

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

The sponsor-provided tabulation of MedDRA preferred term serious and non-serious AEs taken from post-marketing data reporting are included in Table 64. Serious and Non-Serious Adverse Events from Landiolol Post-Market Data. Although it is not possible to know from the available data how many patients were treated with landiolol during the reporting time period from February 3, 2017, through February 2, 2020, included in the table, from August 3, 2016 through February 2, 2022, the sponsor delivered (b) (4) units of landiolol containing 300 mg of landiolol each, which likely represents over (b) (4) treated patients. Assuming these estimations are reasonable, the serious AE rate in the post-market setting is low and no additional clinically relevant AE signals were detected.

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

Table 64. Serious and Non-Serious Adverse Events from Landiolol Post-Market Data

SOC MedDRA PT	Cumulative Frequency (from Feb 3, 2017 – Feb 2, 2020)		
	Spontaneous, Including EU Competent Authorities (worldwide) and Published Literature		Total Spontaneous
	Serious	Non-Serious	
Infections and Infestations			
Sepsis	1	0	1
<i>Subtotal</i>	1	0	1
Nervous system disorders			
Syncope	1	0	1
<i>Subtotal</i>	1	0	1
Cardiac disorders			
Angina pectoris	1	0	1
Bradycardia	2	0	2
Cardiac arrest	2	0	2
<i>Subtotal</i>	5	0	5
Vascular disorders			
Circulatory collapse	1	0	1
Hypotension	2	0	2
<i>Subtotal</i>	3	0	3
General disorders and administration site conditions			
Drug ineffective	1	4	5
<i>Subtotal</i>	1	4	5
Investigations			
Blood pressure decreased	2	2	4
Venous oxygen saturation decreased	0	1	1
<i>Subtotal</i>	2	3	5
Injury, poisoning and procedural complications			
Off label use	0	6	6
Product use issue	0	5	5
<i>Subtotal</i>	0	11	11
Surgical and medical procedures			
Resuscitation	2	0	2
<i>Subtotal</i>	2	0	2
Overall Total	15	21	36

Source: Periodic Safety Update Report (PSUR) #US01 Appendix 2b (Module 5.3.6).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

As described above in Section 8.4.2, the most common Treatment Emergent AEs (TEAEs) consisted of hypotension (Table 56. Frequency of Adverse Events from Landiolol Placebo-Controlled Clinical Trials). To supply further detail, the reported AEs for each included randomized controlled clinical trial are reported subsequently, irrespective of whether they

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride
 were judged to be associated with landiolol administration.

The Kato et al. 1997 publication reports adverse events in 6% of enrolled individuals, with only one episode of decreased BP, as described in Table 65. 'Reduction in blood pressure' and 'reddening of the face' were observed in the same patient; in this case, blood pressure decreased from 102/60 mmHg pre-administration to 80/70 mmHg at the 11th minute of administration and returned to 102/60 mmHg 30 minutes later without additional therapy. All of the adverse events resolved or improved with or without treatment.

Table 65. Adverse events reported in Kato et al. 1997

	Finding	Group A (n = 50)	Group P (n = 49)
Clinical symptoms	Hot flushes	1	0
	Chills	1	0
	Fever	1	0
	BP ↑	1	0
	BP ↓	1	0
	Reddening of the face	1	0
	# observations	6	0
	# Patients (incidence rate)	3 (6.0%)	0
Abnormal change in clinical laboratory values	Na ↓	1	1
	WBC ↑	0	2
	Protein in urine	0	1
	Uric acid ↓	0	1
	RBC ↓	0	1
	Hemoglobin ↓	0	1
	Hematocrit ↓	0	1
	Total protein ↓	0	1
	GOT ↑	0	1
	GPT ↑	0	1
	# observations	1	11
	# Patients (incidence rate)	1 (2.0%)	7 (14.3%)
Total # observations		7	11
Total # patients (incidence rate)		4 (8.0%)	7 (14.3%)
Fisher's exact test		N.S.; p=0.3567	

N.S.: not significant

The Yoshiya et al. 1997 publication reports adverse events in 25 (18%) of enrolled individuals treated with landiolol and 6 (4%) of the enrolled individuals treated with placebo, with only one episode of decreased BP, as described in Table 66, A=landiolol and P=placebo. Hypotension occurred in 18 (13%) of patients treated with landiolol and 1 (<1%) of patients treated with

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

placebo. All of the adverse events resolved or improved with or without treatment.

Table 66. Adverse events reported in Yoshiya et al. 1997

	Symptom	Group A			Group P		
		Overall n = 136	High Risk n = 61	Low Risk n = 75	Overall n = 139	High Risk n = 66	Low Risk n = 73
Subjective and objective symptoms	Hypotension	18	8	10	1	1	-
	Shock	1	1	-	-	-	-
	Respiratory disorder	1	1	-	-	-	-
	Bigeminy	-	-	-	1	-	1
	Multifocal VPC	-	-	-	1	-	1
	ST segment depression	1	1	-	-	-	-
	Increased pulmonary arterial pressure	1	1	-	-	-	-
	Number of adverse events	22	12	10	3	1	2
	Number of patients with adverse events (incidence rate)	21 (15.4%)	11 (18.0%)	10 (13.3%)	2 (1.4%)	1 (1.5%)	1 (1.4%)
Abnormal clinical laboratory values	RBC count ↓	-	-	-	1	-	1
	WBC count ↑	1	-	1	-	-	-
	Platelet count ↓	-	-	-	1	-	1
	Hematocrit ↓	-	-	-	1	-	1
	Hemoglobin ↓	-	-	-	1	-	1
	GPT ↑	1	1	-	-	-	-
	GOT ↑	1	1	-	2	-	2
	LDH ↑	-	-	-	1	-	1
	Total bilirubin ↑	1	1	-	1	-	1
	Total cholesterol ↓	1	-	1	-	-	-
	CPK ↑	-	-	-	1	-	1
	BUN ↓	1	-	1	-	-	-
	Number of adverse events	6	3	3	9	0	9
	Number of patients with adverse events (incidence rate)	4 (2.9%)	1 (1.6%)	3 (4.0%)	4 (2.9%)	0	4 (5.5%)
Total number of adverse events	28			12			
Total number of patients with adverse events (incidence rate)	25 (18.4%)			6 (4.3%)			
Fisher's exact test	***, p=0.0002						

***: p < 0.001

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

The Yoshiya et al. 2002 publication reports adverse events in 19 (70%) of enrolled individuals treated with landiolol and 15 (56%) of the enrolled individuals treated with placebo, with only one episode of decreased BP, as described in Table 67Table 66, A=landiolol and P=placebo. Hypotension occurred in 15 (56%) of patients treated with landiolol and 10 (37%) of patients treated with placebo.

Table 67. Adverse events reported in Yoshiya et al. 2002

Type of adverse event		Group A	Group P
Subjective and objective symptoms	Hypotension	15	10
	Bradycardia	1	0
	ST decrease	1	0
	Negative T-wave	1	1
	Ventricular Premature Contraction (VPC)	2	0
	Atrial fibrillation	1	0
	Disorientation	0	1
	Night delirium	0	1
	Nausea	1	0
	Vomiting	1	1
	Reperfusion syndrome	0	1
	Arteriosclerosis obliterans (ASO)	0	1
	Anaemia	1	1
	Incontinence	0	1
	Headache	1	0
	Fever	2	0
Difficulty with opening sternum due to infection of wound	1	0	
Total	Incidents	28	18
	Patients affected	16	10
	Incidence rate	59.3%	37.0%
Abnormal change in clinical laboratory values	White blood cell count ↑	4	5
	Red blood cell count ↓	3	6
	Hemoglobin ↓	3	7
	Hematocrit ↓	3	7
	Platelet count ↓	3	2
	Total protein ↓	4	9
	Albumin ↓	4	7
	Total bilirubin ↑	1	1
	AST (GOT) ↑	2	4
	ALT (GPT) ↑	0	2
	Alkaline phosphatase ↓	1	1
	LDH ↑	2	1
	LDH ↓	0	1
	Creatinine ↓	1	0
	Total cholesterol ↓	3	2
	CK (CPK) ↑	2	2
CK (CPK) ↓	0	1	
Total	Incidents	36	58
	Patients affected	7	9
	Incidence rate	25.9%	33.3%
Total incidence of adverse events		64	76
Total number of patients affected		19	15
Incidence rate of adverse events		70.4%	55.6%

The Taenaka and Kikawa 2013 publication reports a total of 74 adverse events, 28 adverse events in 11 (20%) of patients treated with placebo, and 46 that occurred in 25 (43%) of

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

patients treated with landiolol. Only those adverse events judged to be related to the study drug are reported in additional detail in the Taenaka and Kikawa 2013 publication, which limits full interpretation of the adverse event profile of landiolol in the enrolled population.

Nonetheless, all the adverse events judged to be related to the study drug were related to the cardiovascular system and the most frequent was hypotension defined by a systolic or diastolic blood pressure $\leq 90/60$ mmHg.

The description of each of the adverse event cases judged to be related to study drug are displayed in Table 68. LM= low dose group, in which a 30 mcg/kg/min bolus was given over 1 minute followed by 10 mcg/kg/min for 10 minutes, then another bolus of 60 mcg/kg/min over 1 minute was given followed by 20 mcg/kg/min for 10 additional minutes if patients had not achieved the primary endpoint of HR reduction. MH= high dose group, in which a 60 mcg/kg/min bolus was given over 1 minute followed by 20 mcg/kg/min for 10 minutes, then a 125 mcg/kg/min bolus dose was given over 1 minute followed by an additional 10 minutes of 40 mcg/kg/min if patients had not achieved the primary endpoint of HR reduction. PP= placebo group.

Each of the cases of hypotension that occurred with landiolol improved with discontinuation of landiolol administration, though some required administration of intravenous crystalloid or colloid solutions, Table 68. For once case procainamide was administered for unclear reasons.

Table 68. Adverse events reported in Taenaka and Kikawa 2013

Treatment group	Content	Onset		Severity	Action taken	Clinical course (time after the onset)
		Time after initiation (min)	Dose developed ADR			
PP	Hypotension	27	Placebo (post)	Mild	No action taken	Resolved (5 min)
	Ventricular extrasystoles	10	Placebo	Mild	No action taken	Resolved (1.2 h)
LM	Hypotension	11	Dose L	Mild	No action taken	Resolved (15 min)
	Hypotension	19	Dose M	Severe	Discontinuation of study drug	Remitted (5 min)
	Hypotension	20	Dose M	Mild	Discontinuation of study drug	Remitted (15 min)
	Hypotension	20	Dose M	Mild	Discontinuation of study drug, administration of plasma protein fraction, blood transfusion	Resolved (26 min)
	Hypotension	26	Dose M (post)	Mild	No action taken	Resolved (5 min)
	Hypotension	36	Dose M (post)	Moderate	Administration of plasma protein fraction	Remitted (15 min)
MH	Hypotension	10	Dose M	Mild	No action taken	Remitted (31 min)
	Hypotension	11	Dose M	Mild	No action taken	Remitted (6 min)
	Hypotension	11	Dose M	Moderate	Discontinuation of study drug, treatment with procainamide hydrochloride	Resolved (30 min)
	Hypotension	18	Dose H	Moderate	Discontinuation of study drug	Resolved (1 h)
	Hypotension	28	Dose H (post)	Mild	No action taken	Resolved (25 min)

The Sakamoto et al. 2012 publication reported adverse events of hypotension and bradycardia with administration of landiolol, defined by BP <90/60 mmHg and HR <60 bpm, respectively. These adverse events are reported for the 71 patients without missing data in Table 69. Of the 35 patients with AF and without missing data treated with landiolol, 4 (11%) experienced hypotension, whereas of the 36 patients without missing data treated with diltiazem, 11 (31%) experienced hypotension. Nevertheless, due to the 13% missing data, or 11 patients enrolled who experienced AF and received one of the study drugs, the rate of adverse events in the landiolol group could have been substantially higher. If all 11 patients with missing data were in the landiolol arm and experienced hypotension, the percentage would be 33%. If only half of the missing patients were in the landiolol arm and all experienced hypotension, then the percentage with hypotension would be 24%. Thus, the Sakamoto et al. 2012 data can be interpreted as implying that the rate of hypotension defined by BP <90/60 mmHg occurring with landiolol therapy in the post-operative management of AF is at least 11%.

Table 69. Adverse events reported in Sakamoto et al. 2012

Table 3. Adverse Effects and Duration of ICU Stay		
	Landiolol (n=35)	Diltiazem (n=36)
Hypotension	4 (11.4)*	11 (30.6)
Bradycardia	0 (0)*	4 (11.1)
Ischemic ECG	0 (0)	2 (5.6)
AV block	0 (0)	0 (0)
Bronchospasm	0 (0)	0 (0)
ICU stay (days)	3.9±2.1	3.4±1.2

Data given as mean±SD or n (%). *P<0.05 vs. diltiazem (χ^2 -test).
 ICU, intensive care unit; ECG, electrocardiogram; AV, atrioventricular.

The Nagai et al. 2013 publication reports that adverse events occurred in 30 (32%) patients in the landiolol treatment arm and 35 (33%) patients in the digoxin treatment arm. At the 2-hour time point, adverse events had occurred in 8 patients treated with landiolol and 2 patients treated with digoxin. Hypotension specifically was identified in 7 patients (7%) in the landiolol group and 4 patients (4%) in the digoxin group, and the landiolol infusion was stopped in 1 patient treated with landiolol due to hypotension. Worsening heart failure occurred in 1 patient treated with landiolol, and another treated with landiolol experienced an embolic stroke. Sinus arrest, diabetes insipidus, and pneumonia each occurred in 1 patient treated with digoxin. The overall incidence of all reported adverse events in Nagai et al. 2013 are included in Table 70.

The patient treated with landiolol who experienced an exacerbation of heart failure developed it 12 hours after completion of the 48-hour administration of landiolol; this same patient died

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride
 31 hours after completion of the administration of landiolol.

Table 70. Adverse events reported in Nagai et al. 2013

Table 2. Incidence of AEs in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin				
	Landiolol (n=93)		Digoxin (n=107)	
	0–2 h	Total	0–2 h	Total
All, n (%)	8 (8.6)	30 (32.2)	2 (1.9)	35 (32.7)
Any serious AE, n (%)	1 (1.1)	2 (2.2)	0 (0)	3 (2.8)
Any AE leading to study drug discontinuation, n (%)	3 (3.2)	3 (3.2)	0 (0)	0 (0)
AEs occurring in >3%, n (%)				
Hypotension	3 (3.2)	7 (7.5)	0 (0)	4 (3.7)
Vomiting	0 (0)	4 (4.3)	0 (0)	1 (0.9)
Nausea	0 (0)	3 (3.2)	0 (0)	0 (0)
Increased creatinine*	0 (0)	3 (3.2)	0 (0)	3 (2.8)
Increased urea*	0 (0)	3 (3.2)	0 (0)	1 (0.9)
Constipation	0 (0)	0 (0)	0 (0)	4 (3.7)

Data are n (%). “0–2 h” included the number of patients with events occurring within 2h after starting treatment. “Total” included the number of patients with events occurring between the start of treatment and the final observation. Only AEs occurring at a frequency of ≥3% are shown.

*Defined as an increase in values from normal to abnormal or worsening of the parameter from baseline; these events were judged by the investigators as an AE based on the clinical significance of the change. AEs, adverse events.

Adverse events in Xiao et al. 2014 are reported in Table 71. In the landiolol group, 7 patients (6%) had hypotension and 1 patient discontinued treatment due to hypotension, while only 1 patient in the placebo group (1%) had hypotension. Hypotension is unfortunately not defined in the publication. The overall rate of adverse events occurred in 11 patients or 9% of those in the landiolol group by 5 minutes of administration, and in 5 patients or 4% of the placebo group. No patients in the placebo group discontinued the study medication due to an adverse event. There were no deaths. There was one episode of sinus bradycardia in the landiolol group.

Table 71. Adverse Events in Xiao et al. 2014

Table 5 Summary of treatment-emergent adverse events

Adverse event, no. (%)	Placebo	Landiolol
	(n = 122)	(n = 118)
Any adverse event	5 (4.10)	11 (9.32)
Hypotension	1 (0.82)	7 (5.93)
Elevated BP	1 (0.82)	2 (1.69)
Elevated total bilirubin	3 (2.46)	0 (0.00)
Elevated alanine aminotransferase, aspartate aminotransferase	0 (0.00)	1 (0.85)
Sinus bradycardia	0 (0.00)	1 (0.85)
Serious adverse event	0 (0.00)	0 (0.00)
Discontinuation due to adverse event	0 (0.00)	1 (0.85)
Significant adverse events ^a	3 (2.46)	7 (5.85)

^a Includes relationship of 'possibly,' 'probably,' 'very likely,' and events with missing relationship.

8.4.6. Laboratory Findings

Laboratory findings with landiolol therapy are discussed in Section 8.3.3 and reported in the tables in Section 8.4.5.

8.4.7. Vital Signs

See Sections 8.4.2 and 8.4.5 for full details as to the BP response following landiolol administration. See Section 7, the Integrated Review of Effectiveness for full details as to the HR response following landiolol administration. As described for each clinical trial in sections and cumulatively for BP in section, landiolol caused a predictable and intended decrease in HR for patients with SVT, with a concomitant predictable decrease in systolic and diastolic BP that resulted in clinical hypotension, most often defined as a BP <90/60 mmHg, in approximately 10% of treated patients (Table 60. Adverse Events and Hypotension in Placebo-Controlled Clinical Treatment Trials of Landiolol).

8.4.8. Electrocardiograms (ECGs)

No clinical trial publication reported which study personnel read the ECGs and whether there were particular criteria used for their interpretation. No primary ECG data were submitted for direct interrogation. While patients were presumably monitored with telemetry or continuous ECG during landiolol administration in the hospitalized setting, there is no description of the monitoring methodology, equipment, or sampling procedures used in the landiolol clinical

trials. In total, at least one parameter was reported for 224 ECGs prior to landiolol administration and 221 ECGs after landiolol administration, as summarized in Table 72. Despite these limited data, landiolol appeared to have only expected effects on ECG parameters, with slowing ventricular rates, prolongation of the PR interval, and mild HR-dependent prolongation of the QT interval, given its mechanism of action. None of the changes in ECG parameters with landiolol treatment are considered to be clinically concerning.

Table 72. Electrocardiograms reported in each landiolol clinical trial

Clinical Trial	Number of ECGs Performed			
	Landiolol		Comparator	
	Pre-administration	On Administration	Pre-administration	On Administration
Kato et al. 1997	37	37	38	38
Yoshiya et al. 1997	105	105	66	66
Yoshiya et al. 2002	21	21	19	19
Tanaka et al. 2008	Not reported	Not reported	Not reported	Not reported
Taenaka and Kikawa 2013	50	48	101	98
Sakamoto et al. 2012	Not reported	Not reported	Not reported	Not reported
Nagai et al. 2013	Not reported	Not reported	Not reported	Not reported

Electrocardiographic parameters were assessed in Kato et al. 1997 prior to drug administration and at 11 minutes of administration. The publication reports ECG parameters for only those patients who did not have termination of their paroxysm of AF or AFL. The RR and QT intervals were prolonged with landiolol treatment compared to placebo as presented in Table 73.

Table 73. Changes in ECG parameters in response to landiolol in Kato et al. 1997

Parameter	Time point of measurement	Group A			Group P			Between-group comparison
		Actual value	Δ	<i>n</i>	Actual value	Δ	<i>n</i>	
RR interval (ms)	Pre-administration	528.8 ± 111.5	-	35	514.8 ± 87.7	-	38	- ***; p=0.0001
	At 11 th minute	681.6 ± 190.1	152.8 ± 137.5	35	527.6 ± 96.3	12.7 ± 44.1	38	
QRS width (ms)	Pre-administration	91.32 ± 29.06	-	37	81.67 ± 18.43	-	42	- N.S.; p=0.6957
	At 11 th minute	91.30 ± 25.26	-0.03 ± 9.14	37	80.98 ± 17.37	-0.69 ± 4.98	42	
QT time (ms)	Pre-administration	320.8 ± 58.8	-	21	323.9 ± 59.9	-	25	- *; p=0.0167
	At 11 th minute	362.3 ± 57.0	41.5 ± 59.5	21	330.4 ± 63.2	6.6 ± 19.9	25	

Mean ± S.D., Between-group comparison of absolute changes from pre-administration value (*t*-test)
 N.S.: not significant, *: *p* < 0.05, ***: *p* < 0.001

Electrocardiographic parameters were assessed in Yoshiya et al. 1997 prior to drug

Clinical Review
 Mitchell Psotka, MD PhD
 NDA 217202
 Landiolol hydrochloride

administration and at 11 minutes of administration, as mean ± standard deviation. The publication reports ECG parameters for only those patients who did not have termination of their paroxysm of SVT. The RR and QT intervals were prolonged with landiolol treatment compared to placebo as presented in Table 74.

Table 74. Changes in ECG parameters with landiolol in Yoshiya et al. 1997

		Time point	Group A			Group P			Comparison (t-test)
			Value	Δ	n	Value	Δ	n	
RR Interval (ms)	Overall	Pre-admin	545 ± 54	—	105	543 ± 53	—	66	***
		After 11 min	744 ± 88	198 ± 87	105	622 ± 96	79 ± 83	66	p=0.0001
	High risk	Pre-admin	536 ± 61	—	45	554 ± 53	—	31	***
		After 11 min	747 ± 104	211 ± 103	45	632 ± 103	78 ± 81	31	p=0.0001
	Low risk	Pre-admin	553 ± 46	—	60	533 ± 51	—	35	***
		After 11 min	741 ± 74	189 ± 73	60	613 ± 89	80 ± 85	35	p=0.0001
PQ time (ms)	Overall	Pre-admin	137 ± 27	—	101	138 ± 27	—	65	***
		After 11 min	149 ± 28	12 ± 17	101	137 ± 29	-1 ± 18	65	p=0.0001
	High risk	Pre-admin	139 ± 27	—	42	147 ± 27	—	31	**
		After 11 min	149 ± 27	10 ± 16	42	145 ± 30	-2 ± 19	31	p=0.0042
	Low risk	Pre-admin	137 ± 27	—	59	130 ± 25	—	34	***
		After 11 min	149 ± 29	13 ± 18	59	130 ± 27	0 ± 17	34	p=0.0008
QRS time (ms)	Overall	Pre-admin	80 ± 17	—	105	81 ± 15	—	66	N.S.
		After 11 min	81 ± 16	2 ± 10	105	83 ± 16	2 ± 9	66	p=0.9069
	High risk	Pre-admin	78 ± 20	—	46	79 ± 15	—	31	N.S.
		After 11 min	80 ± 19	2 ± 9	46	82 ± 14	3 ± 9	31	p=0.6792
	Low risk	Pre-admin	81 ± 14	—	59	83 ± 16	—	35	N.S.
		After 11 min	82 ± 15	1 ± 11	59	83 ± 17	0 ± 9	35	p=0.5934
QT time (ms)	Overall	Pre-admin	338 ± 50	—	104	347 ± 42	—	66	***
		After 11 min	375 ± 53	37 ± 36	104	358 ± 47	11 ± 30	66	p=0.0001
	High risk	Pre-admin	335 ± 58	—	45	350 ± 45	—	31	***
		After 11 min	384 ± 63	49 ± 44	45	362 ± 48	12 ± 30	31	p=0.0001
	Low risk	Pre-admin	340 ± 43	—	59	344 ± 41	—	35	**
		After 11 min	369 ± 43	29 ± 25	59	355 ± 47	11 ± 31	35	p=0.0048
ST (mV)	Overall	Pre-admin	-14 ± 76	—	104	-19 ± 86	—	65	*
		After 11 min	9 ± 60	23 ± 58	104	-15 ± 84	5 ± 45	65	p=0.0250
	High risk	Pre-admin	-30 ± 59	—	45	-40 ± 78	—	30	N.S.
		After 11 min	-11 ± 42	18 ± 48	45	-41 ± 82	-1 ± 48	30	p=0.0922
	Low risk	Pre-admin	-2 ± 86	—	59	-2 ± 89	—	35	N.S.
		After 11 min	24 ± 67	26 ± 66	59	8 ± 80	9 ± 42	35	p=0.1371

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$, N.S.: not significant

Electrocardiographic parameters were assessed in Yoshiya et al. 2002 prior to drug administration and at 11 minutes of administration, as mean ± standard deviation. The RR and QT intervals were prolonged with landiolol treatment compared to placebo as presented in Table 75.

Table 75. Changes in ECG parameters in Yoshiya et al. 2002

		Group A			Group P			t-test for absolute change
		Actual measurement value (mean ± S.D.)	Δ (absolute change) (mean ± S.D.)	n	Actual measurement value (mean ± S.D.)	Δ (absolute change) (mean ± S.D.)	n	
RR interval (s)	Pre-administration	0.530 ± 0.048	-	21	0.562 ± 0.038	-	19	***, p = 0.0001
	At end of administration	0.813 ± 0.126	0.283 ± 0.115	21	0.587 ± 0.060	0.026 ± 0.073	19	
PQ time (s)	Pre-administration	0.152 ± 0.016	-	18	0.158 ± 0.020	-	17	**, p = 0.0025
	At end of administration	0.163 ± 0.017	0.011 ± 0.016	18	0.156 ± 0.018	-0.002 ± 0.007	17	
QRS time (s)	Pre-administration	0.086 ± 0.011	-	21	0.086 ± 0.015	-	19	N.S.; p = 0.9608
	At end of administration	0.087 ± 0.012	0.001 ± 0.004	21	0.087 ± 0.013	0.001 ± 0.008	19	
QT time (s)	Pre-administration	0.369 ± 0.041	-	20	0.378 ± 0.029	-	19	***, p = 0.0001
	At end of administration	0.413 ± 0.031	0.046 ± 0.030	19	0.379 ± 0.031	0.000 ± 0.012	18	
ST value (mV)	Pre-administration	-0.068 ± 0.108	-	21	-0.062 ± 0.150	-	18	N.S.; p = 0.2358
	At end of administration	-0.046 ± 0.095	0.022 ± 0.050	21	-0.076 ± 0.149	0.007 ± 0.026	18	

***: p < 0.001; **: p < 0.01; N.S.: not significant

Electrocardiographic parameters were assessed in Taenaka and Kikawa 2013 prior to drug administration and at 22 minutes at completion of administration, as mean ± standard deviation. The RR, QRS, and QT intervals were prolonged with landiolol treatment compared to placebo, as presented in Table 76.

Table 76. Changes in ECG parameters in Taenaka and Kikawa 2013

	Treatment group									Dunnnett test	
	PP group			LM group			MH group			PP vs. LM	PP vs. MH
	n	Value	Change	n	Value	Change	n	Value	Change		
RR interval											
Pre	50	0.442 ± 0.043		50	0.456 ± 0.040		51	0.458 ± 0.033			
Post	48	0.456 ± 0.052	0.013 ± 0.039	48	0.598 ± 0.059	0.142 ± 0.057	50	0.575 ± 0.086	0.116 ± 0.073	p = 0.0001	p = 0.0001
PQ interval											
Pre	21	0.144 ± 0.024		28	0.141 ± 0.016		28	0.146 ± 0.020			
Post	24	0.148 ± 0.019	0.002 ± 0.012	30	0.155 ± 0.019	0.014 ± 0.017	32	0.163 ± 0.023	0.018 ± 0.017	p = 0.0160	p = 0.0015
QRS duration											
Pre	46	0.083 ± 0.013		47	0.083 ± 0.012		47	0.083 ± 0.010			
Post	46	0.082 ± 0.012	-0.001 ± 0.005	45	0.084 ± 0.013	0.000 ± 0.003	47	0.084 ± 0.010	0.000 ± 0.003	p = 0.0483	p = 0.0483
QT interval											
Pre	30	0.322 ± 0.042		31	0.313 ± 0.039		38	0.306 ± 0.035			
Post	32	0.320 ± 0.035	0.001 ± 0.017	32	0.360 ± 0.051	0.041 ± 0.037	40	0.341 ± 0.043	0.033 ± 0.029	p = 0.0001	p = 0.0001
ST segment											
Pre	33	0.038 ± 0.057		37	0.039 ± 0.041		39	0.064 ± 0.073			
Post	35	0.039 ± 0.057	-0.004 ± 0.023	37	0.041 ± 0.047	-0.001 ± 0.050	39	0.049 ± 0.056	-0.008 ± 0.042	p = 0.9418	p = 0.8979
QTc											
Pre	30	0.478 ± 0.063		31	0.457 ± 0.053		38	0.451 ± 0.049			
Post	32	0.467 ± 0.054	-0.004 ± 0.031	32	0.463 ± 0.056	0.001 ± 0.048	40	0.449 ± 0.049	-0.003 ± 0.034	p = 0.8529	p = 0.9933

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride
8.4.9. **QT**

Landiolol is a beta-1 adrenergic receptor antagonist and was tested in a thorough QT study without substantial QT altering effect. Landiolol metabolites 1 and 2 were also tested. Overall findings were consistent with low risk of Torsades de Pointes due to landiolol. The changes in ECG parameters including QT prolongation with landiolol in the published clinical trials also support the safety of landiolol with regards to the QT interval, as depicted in Table 73, Table 74, Table 75, and Table 76.

8.4.10. **Immunogenicity**

There are not immunogenicity concerns with landiolol.

8.5. **Analysis of Submission-Specific Safety Issues**

8.5.1. **Hypotension**

The most common and clinically relevant adverse event reported with landiolol administration was a reduction in blood pressure with episodes of hypotension, as described in detail in Section 8.4.2, Serious Adverse Events. Although variably defined, and with clinical significance unclear in some cases, hypotension is the expected adverse event for the class of beta-adrenergic receptor antagonists apart from their principal mechanism of action, which is to slow HR. Hypotension occurred at a rate of approximately 10% in landiolol-treated patients with SVT compared to 1.3% for patients with SVT treated with placebo. Although hypotension can be clinically significant, and hypotension long-after the expected resolution of pharmacodynamic effect of landiolol would end was associated with a mortality in the Nagai et al. 2013 clinical trial, given the short duration of action of intravenous landiolol, the predictable association with the effect of BP contemporaneously with change in HR, and the ability to monitor both vital sign changes in the inpatient setting where landiolol is intended to be used support that landiolol can be safely utilized for the treatment of SVT in this setting.

8.6. **Safety Analyses by Demographic Subgroups**

Due to the absence of individual patient data, the occurrence of blood pressure reduction and hypotension could not be analyzed by demographic subgroups.

8.7. **Specific Safety Studies/Clinical Trials**

No randomized clinical trials were performed as specific safety studies.

8.8. **Additional Safety Explorations**

8.8.1. **Human Carcinogenicity or Tumor Development**

Carcinogenicity was not assessed due to the short-term nature of the treatment.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

8.8.2. Human Reproduction and Pregnancy

No known pregnancies or reproductive outcomes, including landiolol use in patients who were lactating, occurred during in any of the published clinical trials using landiolol. There is insufficient clinical data to understand the risk of landiolol to cause developmental adverse outcomes. There is no data that exist regarding the presence of landiolol in human breast milk, its potential effect on a breastfed infant, or on breast milk production.

8.8.3. Pediatrics and Assessment of Effects on Growth

None of the randomized clinical trials submitted as part of the evidence for safety and effectiveness of landiolol enrolled pediatric patients. While Kato et al. 1997 only excluded patients <16 years old, from the reported demographics it appears that the youngest enrolled patient was 21 years old (Table 6). The sponsor has an ongoing clinical trial of landiolol for pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Landiolol does not appear to have potential for abuse. It is expected that cessation of landiolol infusion with concomitant supportive care and vasopressor therapy initiation will be the most expeditious management options in the setting of overdose, but no known overdosing events were reported in any of the clinical trials published for landiolol treatment of SVT. In the clinical trials of landiolol there was no evidence of substantial tachycardic rebound following cessation of landiolol therapy.³⁵

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

No new relevant safety issues have been identified in the most recent Periodic Safety Update Report (PSUR) from 03-Aug-2016 to 02-Feb-2022, as described in more detail in Section 8.9.2. Similar rates of hypotension, at or less than 10%, have been described in the post-marketing setting in this PSUR, which includes an estimate of (b) (4) landiolol-treated patients.

8.9.2. Expectations on Safety in the Postmarket Setting

There is substantial post-market data from Japan and Europe for landiolol and no additional adverse safety signals have been identified. The post-marketing report submission covers the period from 03-Aug-2016 to 02-Feb-2022. The identified risks in those patients are severe

³⁵ Yoshiya I, Ogawa R, Okumura F, et al. Clinical evaluation of landiolol hydrochloride (ONO-1101) on peri-operative supraventricular tachyarrhythmia- a phase III, double-blind study in comparison with placebo. Rinsho Iyaku (Jpn. J. Clin. Therap. Med.) 1997;13(19):4949(129)-4978(158).

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

hypotension, severe bradycardia, and three instances of cardiac arrest. Three cases of cardiac arrest occurred in clinical studies; one in a patient with sick sinus syndrome and was a bradycardic arrest for reported 5-seconds. The outcome of the case was not reported. Two additional cases of cardiac arrest were reported in clinical studies, but with limited additional data, and both patients were reported to have recovered. During the reporting period from 03-Aug-2016 to 02-Feb-2022 three additional cases of cardiac arrest in the estimated (b) (4) patients were reported, one of which occurred 37 hours after completion of landiolol administration but was fatal, one of which occurred in a patient with left ventricular dysfunction who recovered afterwards, and one of which occurred in the setting of likely overdose at approximately 117 mcg/kg bolus compared to the labelled infusion rate of 1- (b) (4) mcg/kg/min.

The absence of the bolus infusion in the proposed label, contrasting with the approved indications in the European Union and Japan, is not expected to alter the safety of landiolol. Based on the information available, a Risk Evaluation and Mitigation Strategy (REMS) does not appear to be necessary to ensure the benefits of landiolol outweigh the risks.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified.

8.10. Integrated Assessment of Safety

Based on the sum of the evidence from multiple randomized controlled clinical trials, including 6 placebo-controlled trials and 2 active-controlled trials, landiolol appears to be safe in the context of cardiac monitoring for reducing HR for patients with SVT including AF and AFL. The principal safety event associated with landiolol administration in the randomized controlled treatment trials, as well as in patients treated for the prevention of SVT and those patients with reported AEs in the post-market setting, is hypotension. In the hospitalized and monitored setting, hypotension is monitorable, and based on the published data, reversible with landiolol discontinuation. Although the clinical trials were performed exclusively outside of the US, principally in Japan and China, the data are clinically applicable to patients in the US, and it is expected that patients in the US will respond similarly to this beta-adrenergic receptor antagonist as they do to other beta-adrenergic receptor antagonists that have supportive data in the US population.

- No individual patient safety data was submitted as part of the application. Safety assessment was only from the published captured adverse events, with the potential for missed ascertainment and no avenue to interrogate the primary medical records, ascertainment protocols, or investigators for the submitted clinical trials.
- The risk of hypotension varied by the population studied in the submitted published data, but no specific predictors of hypotension were identified. Although the inclusion criteria with regards to enrollment BP and HR were not consistently defined, hypotension was in all cases monitorable and reversible.

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

- Although the rate of reported adverse events from large numbers of submitted observational studies was lower, hypotension occurred in 44 of 445 patients included in the randomized placebo-controlled trials, giving a rate of 9.9%, compared to 5 of the 395 patients who received placebo, with a rate of 1.3%. The publications describe the hypotensive effects of landiolol to be monitorable and reversible over the course of 30 minutes with landiolol discontinuation.
- The dose of landiolol utilized for patients with known heart failure was lower than for those patients without heart failure, and the dose was titrated to a lower maximal dose and increased at a slower rate.

Based on the data submitted from 6 randomized placebo-controlled trials and 2 randomized active-controlled trials, landiolol caused a predictable, monitorable, and reversible decrease in blood pressure in the treated populations with associated clinical hypotension. Few patients required landiolol discontinuation due to hypotension, however in the case of discontinuation the hypotension was typically resolved within 30 minutes. The AE of hypotension is thus both clinically monitorable and reversible with landiolol removal. General regulatory understanding of the mechanism of action through beta-adrenergic receptor antagonism and the use of similar medications for this patient population add to the regulatory comfort with this application. Therefore, the applicant has provided substantial evidence of safety of landiolol for the intended population of patients with SVT including patients with AF and AFL, and no additional risk management strategies are required beyond the recommended labeling with expected continuous monitoring of HR and BP in the hospital setting, as well as use of lower dose with slower titration of landiolol for patients with heart failure.

9. Advisory Committee Meeting and Other External Consultations

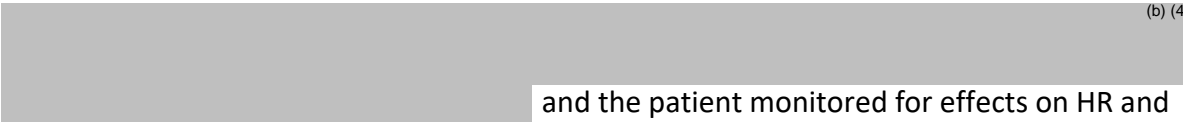
No advisory committee meeting occurred regarding this application, and no other external consultations were undertaken.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

- The proposed label for landiolol is as “a beta-adrenergic blocker indicated for the short-term reduction of ventricular rate in patients with supraventricular tachycardia including atrial fibrillation and atrial flutter.”
- The labelled dosing is that for the free base rather than the landiolol hydrochloride to

maintain consistency in labeling across drug products.

-  (b) (4)
and the patient monitored for effects on HR and BP.
- The proposed starting dose of 10 mcg/kg/min for patients without heart failure, titrated in 10 mcg/kg/min increments according to HR response, to a maximal dose of 40 mcg/kg/min is reasonable in the context of the dosing regimens tested in clinical trials.
- The proposed starting dose of 1 mcg/kg/min for patients with heart failure, titrated in 1 mcg/kg/min increments according to HR response, to a maximal dose of  (b) (4) mcg/kg/min is reasonable in the context of the dosing regimens tested in clinical trials.
- Maintenance infusions are expected to be continued for no longer than 24 hours and the weaning of landiolol and transition to alternative agents should consider the pharmacodynamics of the agent to which the patient is being transitioned.
- The contraindications, warnings, and precautions are those for beta-adrenergic receptor antagonists generally, and the most common adverse reaction was hypotension, occurring in approximately 9.9% of landiolol-treated patients in the published randomized placebo-controlled trial populations.
- Landiolol was demonstrated to be effective at lowering HR for patients with heart failure and left ventricular systolic dysfunction, with left ventricular ejection fraction between 25% and 50% but without systolic BP<90 mmHg, when utilized at a lower dose with slower titration of dosing.
- Due to the risk of hypotension, bradycardia, and worsening cardiac failure, the safety recommendation is to use landiolol in a monitored setting and to monitor for signs and symptoms of cardiovascular adverse effects and reduce or discontinue use if these cardiovascular adverse effects occur.
- Due to the inadequate pharmacologic evaluation of landiolol in patients with hepatic dysfunction, landiolol use should be avoided in patients with Child-Pugh Class B or Class C hepatic dysfunction.

10.2. Nonprescription Drug Labeling

Landiolol is a prescription drug.

11. Risk Evaluation and Mitigation Strategies (REMS)

The risks of landiolol, principally hypotension, can be adequately managed in the postmarket setting through product labeling alone. The hypotension that occurs with landiolol occurs in

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202

Landirolol hydrochloride

approximately 10% of patients and is reversible with product removal. Given the rapid resolution of pharmacologic effect when drug administration is ceased, no additional safety measures are required apart from close monitoring of blood pressure when the drug is administered. A REMS does not appear to be necessary to ensure the benefits of landiolol outweigh the risks.

12. Postmarketing Requirements and Commitments

No postmarketing requirements (PMR) or postmarketing commitments (PMC) are recommended.

13. Appendices

13.1. References

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Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

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Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

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13.2. Financial Disclosure

The applicant submission is based entirely on the published clinical literature and none of the published authors from the submitted clinical trials are financially tied to the current

Clinical Review

Mitchell Psotka, MD PhD

NDA 217202

Landirolol hydrochloride

application. Eight clinical trials were considered as part of the substantial evidence of safety and effectiveness, listed here as Kato et al. (1997), Yoshiya et al. (1997), Yoshiya et al. (2002), Tanaka et al. (2008), Taenaka and Kikawa (2013), Sakamoto et al. (2012), and Nagai et al (2013). Kato et al. (1997) had 12 authors; Yoshiya et al. (1997) had 5 authors, one of whom was an author on Kato et al. (1997); Yoshiya et al. (2002) had 5 authors, 4 of whom were authors on Yoshiya et al. (1997); Tanaka et al. (2008) had 4 authors, Taenaka and Kikawa (2013) had 2 authors; Sakamoto et al. (2012) had 6 authors, Nagai et al. (2013) had 17 authors, 1 of whom was an author on Nagai et al. (2013), and Xiao et al. (2014) had 13 authors. Some of the articles do list their additional site investigators, none of whom are employed or reportedly financially connected to the applicant. The applicant has signed form 3454 indicating no financial arrangement with any of the clinical investigators of the published studies.

Covered Clinical Study (Name and/or Number): Kato et al. (1997), Yoshiya et al. (1997), Yoshiya et al. (2002), Tanaka et al. (2008), and Taenaka and Kikawa et al. (2013), Sakamoto et al. (2012), and Nagai et al (2013), Xiao et al (2014).

Was a list of clinical investigators provided: All manuscript authors were provided, but full investigator lists were not provided.	Yes ☐	No ☒ (Request list from Applicant)
Total number of investigators identified: <u>45</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

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Clinical Review
Mitchell Psotka, MD PhD
NDA 217202
Landiolol hydrochloride

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