Clinical trial results:
Open-label Two-arm PD and PK Study of Landiolol in Patients with Tachycardic Atrial Fibrillation or Atrial Flutter

Summary

EudraCT number	2014-001905-42
Trial protocol	AT
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	09 December 2017
First version publication date	09 December 2017

Trial information

Trial identification

Sponsor protocol code	LDLL600.201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals AG
Sponsor organisation address	Wilhelminenstrasse 91/IIf, Vienna, Austria, A-1160
Public contact	Dr. Michael Zörer, AOP Orphan Pharmaceuticals AG, 0043 1503 72 44-46, michael.zoerer@aoporphan.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2016
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study pharmacodynamics of landiolol (LDLL600) in Caucasian patients with tachycardic atrial fibrillation (AF) or atrial flutter (AFL) treated either according to "alternative" or "conventional" dosing scheme

Protection of trial subjects:

The Investigator obtained a written Informed Consent Form (ICF) from the patients before any screening procedures. Due to the acute clinical condition, exceptions were possible for screening safety laboratory parameters (within 24h). ECG and intravenous catheter insertion was routinely done before the start of the study. To ensure the safety of the patients continuous ECG and haemodynamic monitoring, and an assessment of local tolerability were performed during Landiolol infusion. Patients also completed an End-of-study examination 24 hours after Landiolol infusion discontinuation.
The study was carried out in compliance with the principles of Good Clinical Practice (GCP) and the data protection regulation “Datenschutzgesetz 2000” (DSG 2000).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	9
From 65 to 84 years	10
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients presenting at the out-patient clinic or in-patients with tachycardic AF or AFL were asked to participate in this study.

Pre-assignment

Screening details:

Patients eligible for study participation and landiolol administration were enrolled into the study after giving their written informed consent. A total of 23 patients were screened and a total of 20 patients were enrolled and included.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alternative treatment

Arm description:

Patients treated with alternative dosing scheme.

Arm type	Experimental
Investigational medicinal product name	Landiolol
Investigational medicinal product code	LDLL600
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Continuous infusion of 40 µg/kg/min (maximal total duration of 210 min).

Arm title	Conventional treatment

Arm description:

Patients treated with conventional dosing scheme.

Arm type	Active comparator
Investigational medicinal product name	Landiolol
Investigational medicinal product code	LDLL600
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

Bolus infusion of 100 µg/kg/min for one minute and then continuous infusion of 40 µg/kg/min (maximal total duration of 211 min).

Number of subjects in period 1	Alternative treatment	Conventional treatment
Started	10	10
Completed	10	9
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Alternative treatment
Reporting group description:	
Patients treated with alternative dosing scheme.	
Reporting group title	Conventional treatment
Reporting group description:	
Patients treated with conventional dosing scheme.	

Reporting group values	Alternative treatment	Conventional treatment	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	4	9
From 65-84 years	5	5	10
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	63.9	70.9	
standard deviation	± 7	± 9.9	-
Gender categorical Units: Subjects			
Female	2	6	8
Male	8	4	12
Race Units: Subjects			
Caucasian	10	10	20
AF/AFL Units: Subjects			
AF	9	8	17
AFL	1	2	3
Body mass index Units: kg/m2			
arithmetic mean	27.31	27.62	
standard deviation	± 4.837	± 3.257	-
Height Units: cm			
arithmetic mean	182.7	169.7	
standard deviation	± 7.89	± 10.7	-
Weight			

Units: kg			
arithmetic mean	91.2	80.16	
standard deviation	± 16.685	± 15.923	-
Pre-dose systolic blood pressure			
Units: mmHg			
arithmetic mean	135.2	139.3	
standard deviation	± 20.7	± 17.93	-
Pre-dose heart rate			
Units: bpm			
arithmetic mean	125.8	124.1	
standard deviation	± 16.48	± 13.68	-

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

This set included all patients who received the investigational medicinal product. The evaluation of the primary endpoint - the successful control rate - and the evaluation of the secondary endpoints related to PD or dosing were assessed using this population set.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

This set included all patients who received the investigational medicinal product and was used for analysis of safety and tolerability data.

Subject analysis set title	Per-Protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

This set included all treated patients without major protocol deviations and was used for analysis of PK and PD parameters.

Reporting group values	Full Analysis Set	Safety Set	Per-Protocol set
Number of subjects	20	20	17
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	9	8
From 65-84 years	10	10	8
85 years and over	1	1	1
Age continuous			
Units: years			
arithmetic mean	67.4	67.4	67.2
standard deviation	± 9.09	± 9.09	± 8.53
Gender categorical			
Units: Subjects			
Female	8	8	7

Male	12	12	10

Race Units: Subjects			
Caucasian	20	20	17
AF/AFL Units: Subjects			
AF	17	17	15
AFL	3	3	2
Body mass index Units: kg/m2			
arithmetic mean	27.47	27.47	27.78
standard deviation	± 4.016	± 4.016	± 4.09
Height Units: cm			
arithmetic mean	176.2	176.2	175.9
standard deviation	± 11.32	± 11.32	± 12.02
Weight Units: kg			
arithmetic mean	85.68	85.68	86.51
standard deviation	± 16.854	± 16.854	± 18.024
Pre-dose systolic blood pressure Units: mmHg			
arithmetic mean	137.3	137.3	139
standard deviation	± 18.97	± 18.97	± 17.67
Pre-dose heart rate Units: bpm			
arithmetic mean	125	125	123
standard deviation	± 14.77	± 14.77	± 15.2

End points

End points reporting groups

Reporting group title	Alternative treatment
Reporting group description:	
Patients treated with alternative dosing scheme.	
Reporting group title	Conventional treatment
Reporting group description:	
Patients treated with conventional dosing scheme.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
This set included all patients who received the investigational medicinal product. The evaluation of the primary endpoint - the successful control rate - and the evaluation of the secondary endpoints related to PD or dosing were assessed using this population set.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
This set included all patients who received the investigational medicinal product and was used for analysis of safety and tolerability data.	
Subject analysis set title	Per-Protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
This set included all treated patients without major protocol deviations and was used for analysis of PK and PD parameters.	

Primary: Frequency of patients with successful HR control achieved and maintained during the first 16 min (including) after continuous landiolol infusion start

End point title	Frequency of patients with successful HR control achieved and maintained during the first 16 min (including) after continuous landiolol infusion start
End point description:	
End point type	Primary
End point timeframe:	
Period 1: Overall trial	

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Successful HR control	6	4	10	
Unsuccessful HR control	4	6	10	

Statistical analyses

Statistical analysis title	Comparison of groups
Comparison groups	Alternative treatment v Conventional treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.6563
Method	Fisher exact

Notes:

[1] - Descriptive statistics, exploratory comparative tests.

Secondary: Frequency of patients with successful HR control at any measurement time-point after continuous landiolol infusion start

End point title	Frequency of patients with successful HR control at any measurement time-point after continuous landiolol infusion start

End point description:

End point type	Secondary

End point timeframe:

Period 1: Overall Trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Successful HR control	9	4	13	

Statistical analyses

Statistical analysis title	Comparison of groups
Comparison groups	Alternative treatment v Conventional treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0573
Method	Fisher exact

Notes:

[2] - Descriptive statistics, exploratory comparative tests.

Secondary: Frequency of patients with successful HR control achieved during the first 16 min (including) after continuous infusion start and maintained up to infusion end

End point title	Frequency of patients with successful HR control achieved during the first 16 min (including) after continuous infusion start and maintained up to infusion end

End point description:

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Successful HR control	2	2	4	

Statistical analyses

Statistical analysis title	Comparison of groups
Comparison groups	Alternative treatment v Conventional treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 1
Method	Fisher exact

Notes:

[3] - Descriptive statistics, exploratory comparative tests.

Secondary: Frequency of patients with successful HR control 60 min after continuous landiolol infusion end

End point title	Frequency of patients with successful HR control 60 min after continuous landiolol infusion end

End point description:

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Successful HR control	4	2	6	

Statistical analyses

Statistical analysis title	Comparison of groups
Comparison groups	Conventional treatment v Alternative treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.3498
Method	Fisher exact

Notes:

[4] - Descriptive statistics, exploratory comparative tests.

Secondary: Frequency of patients who converted to sinus rhythm evaluated at any measurement time point

End point title	Frequency of patients who converted to sinus rhythm evaluated at any measurement time point

End point description:

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Converted to sinus rhythm	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to successful HR control

End point title	Time to successful HR control

End point description:

Only patients with HR control included (N=13). The point estimate or limit of confidence interval was not possible to calculate in the "conventional" dosing scheme .

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	8	0[5]	13	
Units: minute				
median (confidence interval 95%)	12 (4 to 16)	(to)	12 (4 to 16)	

Notes:

[5] - The point estimate and limit of confidence interval was not possible to calculate in this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Time-points when dose adjustment or infusion discontinuation is requested and dose administered at this time-points

End point title	Time-points when dose adjustment or infusion discontinuation is requested and dose administered at this time-points

End point description:

Only data with dose change after landiolol infusion start were presented.

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
4 min - Reduction: 20 µg/kg/min	1	0	1	
8 min - Reduction: 20 µg/kg/min	2	0	2	
16 min - Increase: 80 µg/kg/min	3	6	9	
20 min - Increase: 100 µg/kg/min	0	1	1	
30 min - Landiolol terminated	3	6	9	
190 - Reduction: 10 µg/kg/min	3	0	3	
190 min - Reduction: 20 µg/kg/min	3	3	6	
190 min - Reduction: 40 µg/kg/min	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Average dose applied over course of the study

End point title	Average dose applied over course of the study

End point description:

End point type	Secondary

End point timeframe:
Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: µg/kg/min				
arithmetic mean (standard deviation)				
Average dose for individual patient	40.7 (± 18.82)	56.4 (± 16.25)	48.5 (± 18.91)	
Total dose for individual patient	6149 (± 5579.96)	5498 (± 5765.82)	5823.5 (± 5532.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: The frequency of patients with signs of local intolerability

End point title	The frequency of patients with signs of local intolerability

End point description:

End point type	Secondary

End point timeframe:
Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: pts				
Erythema - 60 min, P : <=1 cm	0	1	1	
Erythema - 60 min, P : Negative	10	9	19	
Erythema - EOS : <= 1 cm	0	2	2	
Erythema - EOS : Negative	10	7	17	
Erythema - EOS : Not available	0	1	1	
Pain - IMP end (30 min or 210 min) : Mild	1	0	1	
Pain - IMP end (30 min or 210 min) : Negative	9	10	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Total score of AF/AFL symptoms

End point title	Total score of AF/AFL symptoms

End point description:

The total score was calculated as sum of scores of the following individual symptoms: palpitations, irregular pulse, fatigue, rapid heartbeat, shortness of breath, dizziness and sweating. The overall score ranged between 0 and 7.

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Alternative treatment	Conventional treatment	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10	10	20	
Units: Score				
arithmetic mean (standard deviation)				
Pre-dose	2.5 (± 2.42)	3.2 (± 1.32)	2.9 (± 1.93)	
16 min	1 (± 1.33)	0.6 (± 0.84)	0.8 (± 1.11)	
30 min	0.6 (± 1.13)	0.8 (± 0.96)	0.6 (± 1.03)	
Landiolol end, 30 min	1.7 (± 0.58)	0.5 (± 0.84)	0.9 (± 0.93)	
Landiolol end, 210 min	0.1 (± 0.38)	0.3 (± 0.5)	0.2 (± 0.4)	
EOS	1.1 (± 1.66)	1.1 (± 2.1)	1.1 (± 1.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameters of Landiolol

End point title	Pharmacokinetic parameters of Landiolol

End point description:

End point type	Secondary

End point timeframe:

Period 1: Overall trial

End point values	Per-Protocol set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: µg/mL				
arithmetic mean (standard deviation)				

Cmax (µg/mL)	1.717 (± 0.8676)			
tmax (h)	0.963 (± 1.0763)			
Cmax (till HR success) (µg/mL)	0.815 (± 0.5156)			
AUC(0-t) (µg*h/mL)	1.923 (± 1.4393)			
AUC(0-t) (till HR success) (µg*h/mL)	0.108 (± 0.1625)			
λz (h^-1)	8.693 (± 2.1835)			
AUC(0-inf) (µg*h/mL)	1.926 (± 1.439)			
Residual area (%)	0.24 (± 0.261)			
t1/2 (min)	5.042 (± 1.1464)			
Total body clearance (CL) [mL/(kg*h)]	2431.5 (± 805.623)			
Volume of distribution (Vd) [mL/kg]	289.86 (± 118.383)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing the informed consent form until follow-up visit.	
Adverse event reporting additional description:	
Check for adverse events was performed during IMP infusion, 60 min after IMP infusion end and on End-of-Study visit (1 day after IMP infusion).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Alternative dosing scheme
Reporting group description:	
Subjects starting with 40 µg/kg/min continuous infusion.	
Reporting group title	Concentional dosing scheme
Reporting group description:	
Subjects starting with one minute of 100 µg/kg/min bolus infusion and continuing with 40 µg/kg/min continuous infusion.	

Serious adverse events	Alternative dosing scheme	Concentional dosing scheme	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Alternative dosing scheme	Concentional dosing scheme	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	4 / 10 (40.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Hypotension			
subjects affected / exposed	3 / 10 (30.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Injection site pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2014	The inclusion criterion n°2 (SBP ≥ 95 mmHg) was changed into SBP ≥ 100 mmHg. Correspondingly, the exclusion criterion n°1 (SBP 95 mmHg) was changed into SBP 100 mmHg.
28 January 2015	The exclusion criteria n°9 (Any ivabradine, antiarrhythmic and/or calcium channel blocker within the last 12h) and n°10 (Amiodarone therapy within the last 4 weeks) were suppressed. The blood sampling for amiodarone serum level assessment was added for patients pre-treated with amiodarone any time prior to first dose of landiolol. Concomitant medications were allowed except for ivabradine, amiodarone and/or calcium channel blocker administration "during investigational medicinal product infusion duration". Then, subgroup or sensitivity analysis was planned to assess the effect of ivabradine, amiodarone and/or calcium channel blocker on PD/PK evaluation and safety.
24 June 2015	An additional arm was implemented ("conventional treatment arm": one min of 100 µg/kg/min bolus infusion before switching to continuous infusion scheme with a dosing of 40 µg/kg/min). Then, the title of the study was modified: the "single-arm study" became the "two-arm" study as in the body of the Protocol. The term "monocentre" was deleted. The schedule of activities and regular dosing scheme during treatment were changed. The design of the study included now a pilot phase and a planned randomized phase. In the pilot phase, the first set of patients was to be treated with the "alternative dosing scheme" (40 µg/kg/min continuous infusion). Thereafter, the patients were to be treated with the "conventional dosing scheme". Then, the patients were to be allocated to one of the two study arms in ratio 1:1. Depending on achievement of successful heart rate control, the dose was maintained, increased or reduced (according to the updated regular dosing scheme in appendix 3). The planned maximal continuous infusion duration was 180 min plus 30 min switch phase to oral therapy (210 min in total). Patients treated with "conventional" dosing scheme received a bolus infusion for one minute upfront resulting in 211 min total landiolol infusion. The dosing scheme was simplified: no mandatory dose reductions up to minute 16 and the sampling time point at minute 2 was deleted. In the same way, LTA was done at baseline, at the end of infusion, 60 min after the end of infusion and at follow-up visit. The primary objective was now to study PD of landiolol in Caucasian patients with tachycardic AF or AFL treated either according to the "alternative" or the "conventional" dosing scheme. The secondary objectives were now to study PK, tolerability and safety of the "alternative" and "conventional" landiolol dosing scheme in those patients. The study endpoints were changed accordingly. Enrolment duration changed to 15 months. Statistical methods were performed by study arms.
28 August 2015	An additional site was nominated (Prof. Lueger, Graz). Some laboratory parameters were removed from the schedule of assessments (prothrombine time [PT, INR, including PT-ratio], aPTT-ratio, cholesterol, total protein and albumin). The time points 45, 75, 90 and 150 min were added (including HR, ECG, BP, AE checks)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported