Clinical trial results:
Randomized, open-label, controlled study on the efficacy of Ciclopoli® (ciclopirox 8% nail lacquer) versus Loceryl® (amorolfine 5% nail lacquer) on the culture conversion to negative in patients with onychomycosis

Summary

EudraCT number	2011-003087-70
Trial protocol	LV
Global end of trial date	27 May 2014

Results information

Result version number	v1 (current)
This version publication date	05 January 2017
First version publication date	05 January 2017

Trial information

Trial identification

Sponsor protocol code	PM1125

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Polichem S.A.
Sponsor organisation address	50, Val Fleuri, Luxembourg, Luxembourg,
Public contact	Maurizio Caserini, Polichem S.A., 0041 919864000, maurizio.caserini@polichem.com
Scientific contact	Maurizio Caserini, Polichem S.A., 0041 919864000, maurizio.caserini@polichem.com

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	04 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2014
Global end of trial reached?	Yes
Global end of trial date	27 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Ciclopoli® (ciclopirox 8%, coded as P-3051) water soluble nail lacquer and Loceryl® (amorolfine 5%) water insoluble nail lacquer in the conversion to negative of culture evaluated at week 12.

All results data are based on the Intention-to-Treat population (ITT): all randomized patients who received at least one dose of the investigational medicinal product, with baseline evaluation and with at least one post-baseline efficacy measurement, i.e. any post-baseline measurement of primary efficacy variable.
N (ITT 12w) = 137; N (ITT 48w) = 120.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Prior to study start, patients received a full explanation of the aims of the study, benefits, potential discomforts and risks of taking part in the study. A written explanation was provided in the study information sheet at the screening visit or before. The written informed consent was then obtained before any study procedure was started.

Background therapy: -

Evidence for comparator:

No data are available yet on the kinetic of culture conversion to negative of 8% ciclopirox-medicated nail lacquer and of amorolfine 5% nail lacquer in the first three months of treatment. The aim of this phase III study is to evaluate the kinetic of culture conversion to negative of 8% ciclopirox-medicated nail lacquer administered according to Summary of Product Characteristics (SPC) compared to amorolfine administered according to SPC in patients affected by mild-tomoderate, distal sub-ungual onychomycosis of the toenails in the first three, six and twelve treatment months.

Actual start date of recruitment	21 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Latvia: 120
Worldwide total number of subjects	137
EEA total number of subjects	120

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)	121
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with mild-to-moderate distal subungual onychomycosis (without lunula involvement) due to fungal nail pathogens (dermatophytes, white yeasts and/or Scopulariopsis spp. and/or Fusarium spp.) confirmed by the culture affecting at least one big toenail were recruited.

Pre-assignment

Screening details:

Patients fulfilling the inclusion criteria entered the study and were randomly allocated in a balanced randomisation (1:1 ratio) to one out of the two treatment groups.

Period 1

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

Blinding implementation details:

The study was on two arms with an open label design. The different posology (once a day of P-3051 vs twice a week of amorolfine 5%) had not allowed to design a double-blind study. In order to overcome this limitation, the protocol foresaw to do, at the end of the study, a blind evaluation of pictures and computerized planimetry data by the International Scientific Study Coordinator, who gave an unbiased judgement, of secondary endpoints had been reached for each patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Ciclopoli® Nagellack

Arm type	Experimental
Investigational medicinal product name	Ciclopirox 8% nail lacquer
Investigational medicinal product code	P-3051
Other name	Ciclopoli® Nagellack
Pharmaceutical forms	Medicated nail lacquer
Routes of administration	Topical use

Dosage and administration details:

Used batch: Latvia, 9290A (expiry date: 06/2014); Russia, 11160A (expiry date 11/2015).
To be applied once a day, according to the approved leaflet.

Arm title	Group B

Arm description:

Loceryl® Wirkstoffhaltiger Nagellack

Arm type	Active comparator
Investigational medicinal product name	Amorolfine 5% nail lacquer
Investigational medicinal product code	
Other name	Loceryl® Wirkstoffhaltiger Nagellack
Pharmaceutical forms	Medicated nail lacquer
Routes of administration	Topical use

Dosage and administration details:

Used batches: Latvia, 1212212 (expiry date 08/2014); Russia, 2212221 (expiry date 07/2015).
To be applied twice a week, according to the approved leaflet.

Number of subjects in period 1	Group A	Group B
Started	69	68
Completed	64	67
Not completed	5	1
Protocol deviation	5	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description: Ciclopoli® Nagellack	
Reporting group title	Group B
Reporting group description: Loceryl® Wirkstoffhaltiger Nagellack	

Reporting group values	Group A	Group B	Total
Number of subjects	69	68	137
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)	62	59	121
From 65-84 years	7	9	16
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.64	52.91	
standard deviation	± 11.3	± 13.07	-
Gender categorical Units: Subjects			
Female	56	54	110
Male	13	14	27

End points

End points reporting groups	
Reporting group title	Group A
Reporting group description: Ciclopoli® Nagellack	
Reporting group title	Group B
Reporting group description: Loceryl® Wirkstoffhaltiger Nagellack	

Primary: Conversion to negative of culture evaluated at 12 weeks	
End point title	Conversion to negative of culture evaluated at 12 weeks
End point description:	
End point type	Primary
End point timeframe: From baseline to Week 12.	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: number of patients with negative result	54	44		

Statistical analyses

Statistical analysis title	Comparisons between groups at Week 12
Comparison groups	Group A v Group B
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.079
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.285

Notes:

[1] - The comparison between groups at week 12 showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.136. The 95% CI of the difference between groups was -0.014 to 0.285, and lied entirely above the pre-specified limit of -9%, thus showing that P-3051 was

not inferior to amorolfine 5%. The difference between groups was not statistically significant (P = 0.079).

Secondary: Conversion to negative of culture evaluated at 4 and 8 weeks	
End point title	Conversion to negative of culture evaluated at 4 and 8 weeks
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to Week 4 and Week 8.	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: number of patients with negative result				
Week 4	12	7		
Week 8	25	9		

Statistical analyses

Statistical analysis title	Comparisons between groups at Week 4
Comparison groups	Group A v Group B
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.229
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.186

Notes:

[2] - The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.071. The 95% CI of the difference between groups was -0.044 to 0.186, thus showing that the difference between groups was not statistically significant (P = 0.229).

Statistical analysis title	Comparisons between groups at Week 8
Comparison groups	Group A v Group B

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.002
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.091
upper limit	0.369

Notes:

[3] - The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.230. The 95% CI of the difference between groups was 0.091 to 0.369, thus showing that the difference between groups was statistically significant (P = 0.002), in favour of the P-3051 group.

Secondary: Conversion to negative of microscopy

End point title	Conversion to negative of microscopy
End point description:	
Conversion to negative of microscopy using Potassium Hydroxide (KOH) preparation.	
End point type	Secondary
End point timeframe:	
At Week 8 and Week 12.	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: patients with a negative result				
Week 4	2	0		
Week 8	18	2		
Week 12	44	37		

Statistical analyses

Statistical analysis title	Comparisons between groups at Week 8
Comparison groups	Group A v Group B
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.0001
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.231

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.343

Notes:

[4] - The results at week 8 showed that conversion to negative of microscopy (KOH) was observed in 18 patients (26.1%) in the P-3051 group and in 2 (2.9%) in the amorolfine 5% group. The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.231. The 95% CI of the difference between groups was 0.120 to 0.343, thus showing that the difference between groups was statistically significant (P = 0.0001), in favour of the P-3051 group.

Statistical analysis title	Comparisons between groups at Week 12
Comparison groups	Group A v Group B
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.265
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.258

Notes:

[5] - The results at week 12 showed that conversion to negative of microscopy (KOH) was observed in 44 patients (63.8%) in the P-3051 group and in 37 (54.4%) in the amorolfine 5% group. The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.094. The 95% CI of the difference between groups was -0.070 to 0.258, thus showing that the difference between groups was not statistically significant (P = 0.265).

Secondary: Determination of nail infected area compared to baseline

End point title	Determination of nail infected area compared to baseline

End point description:

Results of percent decrease from baseline of nail infected area by visit.

End point type	Secondary

End point timeframe:

From baseline to Week 4, Week 8 and Week 12.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: percent				
arithmetic mean (standard deviation)				
Week 4	-6.27 (± 14.19)	-7.12 (± 14.54)		
Week 8	-14.94 (± 20.44)	-17.39 (± 21.03)		

Week 12	-30.02 (± 24.99)	-27.17 (± 27.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Determination of growth rate of healthy nail

End point title	Determination of growth rate of healthy nail

End point description:

Changes from baseline in healthy area of the target big toenail by visit.

End point type	Secondary

End point timeframe:

From baseline to Week 4, Week 8 and Week 12.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: increase of healthy area				
arithmetic mean (standard deviation)				
Week 4	3.1 (± 7.31)	3.47 (± 6.65)		
Week 8	6.71 (± 9.17)	8 (± 9.56)		
Week 12	12.75 (± 11.27)	12.69 (± 12.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Responders rate at week 12

End point title	Responders rate at week 12

End point description:

Patients with conversion to negative of culture and of microscopic KOH examination and with decrease of affected nail area to ≤10% of total.

End point type	Secondary

End point timeframe:

At Week 12.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: number of responders	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete cure rate at week 12

End point title	Complete cure rate at week 12

End point description:

Complete replacement of the affected nail by new healthy nail, accompanied by conversion to negative of culture and of microscopic KOH examination.

End point type	Secondary

End point timeframe:

At Week 12.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: number of patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete cure rate at week 48

End point title	Complete cure rate at week 48

End point description:

Complete replacement of the affected nail by new healthy nail, accompanied by conversion to negative of culture and of microscopic KOH examination.

End point type	Secondary

End point timeframe:

At Week 48.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of patients	21	7		

Statistical analyses

Statistical analysis title	Comparison between groups at week 48
Comparison groups	Group A v Group B
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Mean difference (net)
Point estimate	0.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.379

Notes:

[6] - The results at week 48 showed that complete cure was observed in 21 patients (35.0%) in the P-3051 group and in 7 (11.7%) in the amorolfine 5% group. The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.233. The 95% CI of the difference between groups was 0.088 to 0.379, thus showing that the difference between groups was statistically significant (P < 0.001), in favour of the P-3051 group.

Secondary: Responders rate at week 48

End point title	Responders rate at week 48

End point description:

Patients with conversion to negative of culture and of microscopic KOH examination and with decrease of affected nail area to ≤10% of total.

End point type	Secondary

End point timeframe:

At Week 48.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: number of responders	35	16		

Statistical analyses

Statistical analysis title	Comparison between groups at week 48
Comparison groups	Group A v Group B
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Median difference (net)
Point estimate	0.317
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.484

Notes:

[7] - The results at week 48 showed that response was observed in 35 patients (58.3%) in the P-3051 group and in 16 (26.7%) in the amorolfine 5% group. The comparison between groups showed that the difference between the P-3051 group and the amorolfine 5% group was equal to 0.317. The 95% CI of the difference between groups was 0.149 to 0.484, thus showing that the difference between groups was statistically significant (P < 0.001), in favour of the P-3051 group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety was monitored throughout the whole study period, from screening to discontinuation visit, by recording any adverse event (AE).

Adverse event reporting additional description:

AEs are described considering the safety population: all randomized subjects who received at least one dose of the study products.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	P-3051

Reporting group description: -

Reporting group title	Amorolfine 5%

Reporting group description: -

Serious adverse events	P-3051	Amorolfine 5%	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 69 (0.00%)	0 / 68 (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	P-3051	Amorolfine 5%	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 69 (31.88%)	23 / 68 (33.82%)	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Heat stroke			
subjects affected / exposed	1 / 69 (1.45%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Limb injury			

subjects affected / exposed	3 / 69 (4.35%)	1 / 68 (1.47%)	
occurrences (all)	3	1	
Traumatic haematoma			
subjects affected / exposed	1 / 69 (1.45%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 69 (1.45%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Nail operation			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 69 (11.59%)	11 / 68 (16.18%)	
occurrences (all)	9	14	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 69 (1.45%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 69 (1.45%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 69 (2.90%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Cystitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Helicobacter gastritis			

subjects affected / exposed	1 / 69 (1.45%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 69 (1.45%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Laryngitis			
subjects affected / exposed	1 / 69 (1.45%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	0 / 69 (0.00%)	4 / 68 (5.88%)	
occurrences (all)	0	4	
Rhinitis			
subjects affected / exposed	2 / 69 (2.90%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Tooth abscess			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2012	Substantial amendment No. 1 (all sites): At the time of the protocol design, no data of superiority of amorolfine 5% drug versus placebo or non-inferiority versus active comparator, had ever been published. Therefore, the collection of clinical and mycological data after 6 and 12 months of treatment was originally included in the protocol as secondary endpoints. New studies at the end of 2011 presented the results of mycological cure with amorolfine at the end of the treatment period (48 weeks). Therefore these publications made available the results of secondary endpoints scheduled in the study protocol that were unavailable at the time of the protocol writing. In order to focalize the study on the primary end-point of the study (kinetic of culture conversion to negative of 8% ciclopirox-medicated nail lacquer and of amorolfine 5% nail lacquer in the first 3 months of treatment), the protocol was amended by deleting the evaluation planned after the further 9 months of treatment. Due to regulatory purposes, the study was conducted with an assumption of non-inferiority in place of the original hypothesis of superiority (with the corresponding change in the statistical part). Furthermore, with this amendment the number of sites was increased by adding new sites in Russia.
24 September 2012	Substantial amendment No. 2 (country specific: Latvia): After the amendment No. 1 and with the deletion of the evaluations at 24 and 48 weeks, it was specifically requested, due to ethical reason, that the study would have guaranteed to the patients a treatment course for onychomycosis of 48 weeks, as recommended by international guidelines. Thus, once the patients completed the three months of treatment foreseen as primary endpoint by the original protocol and as secondary endpoints scheduled by Protocol amendment No. 1, they entered in a 9-month "active follow up phase", provided with the needed drugs. Based on this amendment, the safety, efficacy and tolerability data, collected after 24 and 48 weeks of treatment in the Latvian centre have been presented in a separate analysis and described in this integrative report.
01 February 2014	Non-substantial amendment No. 3 (country specific: Latvia): This non-substantial amendment regarded the specification of the responsibility for the evaluation of the pictures inserted in the electronic case report form (eCRF), related the progression of the disease in the patients enrolled, and data used for the evaluation of the secondary study endpoints. Therefore, in order to guarantee the homogeneity of the evaluations and to improve the scientific value of the trial, an external parallel evaluation in blind, performed by an independent Medical Expert (Central Blinded Assessor) was scheduled. Only data from the Latvian centre derived this central evaluation were used for the final statistical analysis. Deviations in the non-substantial amendment No. 3 occurred in the final analysis. In fact, the Blinded Assessor evaluated the progression of the disease of all patients enrolled, but produced a report related to Visits 6 and 7 (24 and 48 weeks, respectively) only, due to the fact that a responsiveness/cure was unlikely reached within 12 weeks of treatment only as per disease conditions.

14 May 2014	Non-substantial amendment No. 4 (country specific: Latvia): This non-substantial amendment regarded the decision of not performing of the exploratory objective of the study (evaluation of nail concentration of ciclopirox and amorolfine) initially planned in the study protocol, by collecting patients' nail samples. The Sponsor decided not to perform this examination because in a very recent paper published by Monti et al (18 - the data, not available when the protocol was written, have been reported). Consequently, the examination has been deleted for futility. On the other hand, with this amendment and according to the exclusion criteria reported in the study protocol, the Sponsor intended to detect the use of systemic terbinafine (the most common systemic drug for the treatment of onychomycosis) on the affected nail, at the end of treatment, analysing the samples initially collected for the PK analysis. Those patients with a detectable terbinafine concentration above 0.9 µg/mL, which corresponds to the nail terbinafine concentration after a 16 and 30 days oral terbinafine multiple-dose administration, according to the paper of Kovarik et al (17), were excluded from the PP population at 12 and 48 weeks during the statistical analysis of the results of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27171791