Clinical trial results:
BENDAMUSTINE, LENALIDOMIDE AND RITUXIMAB (R2-B) COMBINATION AS A SECOND-LINE THERAPY FOR FIRST RELAPSED-REFRACTORY MANTLE CELL LYMPHOMAS: A PHASE II STUDY

Summary

EudraCT number	2011-005461-21
Trial protocol	IT
Global end of trial date	02 February 2017

Results information

Result version number	v1 (current)
This version publication date	12 June 2022
First version publication date	12 June 2022

Trial information

Trial identification

Sponsor protocol code	FILR2-B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01737177
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione Italiana Linfomi (FIL) ONLUS
Sponsor organisation address	Piazza Turati 5, Alessandria, Italy,
Public contact	Segreteria, Fondazione Italiana Linfomi Onlus, +39 0131/033151, segreteriadirezione@filinf.it
Scientific contact	Segreteria, Fondazione Italiana Linfomi Onlus, +39 0131/033151, segreteriadirezione@filinf.it

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	31 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	Yes
Global end of trial date	02 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To explore the antitumor activity of the association of R2-B in terms of complete response (CR) in patients with relapsed/refractory MCL to a first line of therapy.

2. To evaluate the efficacy of a maintenance treatment with Lenalidomide for 18 months from the end of R2-B (from month 7 to 24) for those responding (CR or PR) to the induction, in terms of progression free survival (maPFS).

Protection of trial subjects:

INDUCTION PHASE
Lenalidomide dose modification according to hematological and extrahematological toxicity is allowed. Patients who can not tolerate the dose of 5 mg daily will prosecute the induction phase only with Rituximab and Bendamustine.
If Lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. No dose (re-)escalation is permitted at any time.
Those patients for whom Lenalidomide dose reduction is not sufficient and require also a reduction in the dose of Bendamustine, they will interrupt treatment, they will be considered failure and they will be treated according to the single centre policy. Bendamustine dose reduction is not allowed.
Rituximab dose reduction is not planned.

CONSOLIDATION PHASE
Lenalidomide dose modification according to hematological and extrahematological toxicity is allowed. The minimum dose permitted is 5 mg daily. Patients who can not tolerate this dose will interrupt treatment. If Lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. No dose (re-)escalation is permitted at any time.
Rituximab dose reduction is not planned.

MAINTENANCE PHASE
Permitted lenalidomide dose modifications during the maintenance phase are similar to those in the consolidation phase.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2012
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	Italy: 42

Worldwide total number of subjects	42
EEA total number of subjects	42

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)	11
From 65 to 84 years	30
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between July 2012 and June 2013, 42 patients were enrolled in Italian centers.

Pre-assignment

Screening details:

Patients with MCL relapsed or refractory after a first line of chemotherapy.
All patients must satisfy all the inclusion criteria and none of exclusion criteria.

Period 1

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

Arms

Arm title	Single arm

Arm description:

R2-B treatment will be repeated for two cycles every 28 days, then patients will be evaluated for response; in case of CR, PR or SD, they will prosecute treatment for further two cycles. Patients after the end of the induction phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR and PR at the end of the induction phase, will continue therapy with a consolidation phase, that includes combination therapy with Lenalidomide and Rituximab (R2) every 28 days for 2 cycles.
Patients after the end of the consolidation phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR or PR at the end of the consolidation treatment will continue to a maintenance phase with Lenalidomide until disease progression or unacceptable toxicity up to 18 months, with 28-days cycles

Arm type	Single arm study
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

INDUCTION PHASE (COURSE 1-4)
Bendamustine: 70 mg/m2 on day 2 and 3 every 28

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

INDUCTION PHASE (COURSE 1-4)
Lenalidomide: 10 mg/daily on day 1 to 14 of a 28 days course

CONSOLIDATION PHASE (courses 5-6)
Lenalidomide: 15 mg/daily on day 1 to 21 of a 28 days course

MAINTENANCE PHASE (courses 7-24)
Lenalidomide: 15 mg/daily on day 1 to 21 of a 28 days

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Infusion

Dosage and administration details:

INDUCTION PHASE (COURSE 1-4)
Rituximab: 375 mg/m2 on day 1 every 28 days; only for the first cycle in the induction phase will start on day 8

CONSOLIDATION PHASE (courses 5-6)
Rituximab: 375 mg/m2 on day 1 every 28 days

Number of subjects in period 1	Single arm
Started	42
Completed	15
Not completed	27
Adverse Event	8
Other	2
Progression	16
SD after induction	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	30	30	
85 years and over	1	1	
Age continuous Units: years			
median	70		
inter-quartile range (Q1-Q3)	64 to 76	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	31	31	
1st line Therapy Units: Subjects			
R-CHOP o R-CHOP like	27	27	
Regimen containing ARA-C	3	3	
Regimen containing Fludarabine	2	2	
ASCT	10	10	
Clinical Response to 1st line therapy Units: Subjects			
CR	30	30	
PR	8	8	
SD	2	2	
PD	2	2	
Histology Units: Subjects			
MCL Classic	41	41	
MCL Blastoid	1	1	
B Symptomes Units: Subjects			
Yes	6	6	
No	36	36	
ECOG Performance status Units: Subjects			
ECOG 0	25	25	
ECOG 1	15	15	
ECOG 2	2	2	
Stage Units: Subjects			

Stage I	1	1	
Stage II	2	2	
Stage III	7	7	
Stage IV	32	32	
Bone Envolvment Units: Subjects			
Neg	21	21	
Pos	18	18	
Not Evaluable	3	3	
Mediastinal syndrome Units: Subjects			
Yes	1	1	
No	41	41	
IPI Units: Subjects			
IPI 1	4	4	
IPI 2	18	18	
IPI 3	18	18	
IPI 5	2	2	
Ki67 Units: Subjects			
<10	1	1	
20-30	6	6	
>30	10	10	
Not recorded	25	25	
Duration of response (months) Units: Subjects			
<12	11	11	
12-24	12	12	
>24	14	14	
Not recorded	5	5	
MIPI Units: Score			
median	4		
inter-quartile range (Q1-Q3)	3 to 6	-	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

R2-B treatment will be repeated for two cycles every 28 days, then patients will be evaluated for response; in case of CR, PR or SD, they will prosecute treatment for further two cycles. Patients after the end of the induction phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR and PR at the end of the induction phase, will continue therapy with a consolidation phase, that includes combination therapy with Lenalidomide and Rituximab (R2) every 28 days for 2 cycles.
Patients after the end of the consolidation phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR or PR at the end of the consolidation treatment will continue to a maintenance phase with Lenalidomide until disease progression or unacceptable toxicity up to 18 months, with 28-days cycles

Subject analysis set title	Subject analyzed
Subject analysis set type	Full analysis

Subject analysis set description:

Between July 2012 and June 2013, 42 patients were enrolled in Italian centers

Primary: CR proportion after Induction/Consolidation phase

End point title	CR proportion after Induction/Consolidation phase

End point description:

Proportion of CR according to the Cheson2007 response criteria

End point type	Primary

End point timeframe:

After Induction/Consolidation phase. At the end of the consolidation phase (6 months)

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	42		
Units: Number of patients				
CR	23	23		

Statistical analyses

Statistical analysis title	CR proportion after Induction/Consolidation phase
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Frequency percent (%)
Point estimate	55

Confidence interval	
level	95 %
sides	1-sided
lower limit	41

Primary: Maintenance Progression Free Survival (maPFS)

End point title	Maintenance Progression Free Survival (maPFS)

End point description:

The maPFS in the subset of patients with CR or PR, receiving the maintenance regimen. maPFS in the maintenance cohort will be defined as the time between the date of CR/PR and the date of disease progression or death from any cause. Patients without events will be censored at the last follow up visit

End point type	Primary

End point timeframe:

Up to 36 months

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	42		
Units: Probability				
number (not applicable)	60.3	60.3		

Statistical analyses

Statistical analysis title	maPFS for CR/PR patients after consolidation

Statistical analysis description:

Time-to-event variables were analysed using the Kaplan-Meier method.

Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan Meier estimates
Point estimate	60.3
Confidence interval	
level	95 %
sides	1-sided
lower limit	43.3

Secondary: ORR after Induction/Consolidation phase

End point title	ORR after Induction/Consolidation phase

End point description:

Overall response rate (CR+PR) will be assessed at the end of the consolidation treatment

End point type	Secondary
End point timeframe:	
After Induction/Consolidation phase	

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	42		
Units: number of patients				
CR/PR	33	33		

Statistical analyses

Statistical analysis title	Overall Response Rate (ORR)
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Frequency percent (%)
Point estimate	79
Confidence interval	
level	95 %
sides	2-sided
lower limit	63
upper limit	90

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description:	
Progression Free Survival (PFS) in all patients will be defined as the time between the date of enrolment and the date of recurrence/disease progression or death from any cause. Patients without events will be censored at the last follow up visit.	
End point type	Secondary
End point timeframe:	
2-years	

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	42		
Units: 2-year probability				
number (confidence interval 95%)	47.7 (27.7 to 57.0)	47.7 (27.7 to 57.0)		

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)
Statistical analysis description: Time-to-event variables were analysed using the Kaplan-Meier method.	
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	2- years PFS
Point estimate	47.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.7
upper limit	57

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: Overall Survival (OS) will be defined as the time between the date of enrollement (or the date of the end of consolidation for the maintenance cohort) and the date of death from any cause. Patients alive at the end of follow-up will be censored at the last follow up visit.	
End point type	Secondary
End point timeframe: 2-year	

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	42	42		
Units: 2-year probability				
number (confidence interval 95%)	66.7 (50.3 to 78.7)	66.7 (50.3 to 78.7)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Statistical analysis description:	
Time-to-event variables were analysed using the Kaplan-Meier method.	
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan Meier estimates
Point estimate	66.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.3
upper limit	78.7

Secondary: Safety evaluation induction

End point title	Safety evaluation induction
End point description:	
Any grade III or higher toxicities will be recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (October 1, 2009).	
End point type	Secondary
End point timeframe:	
After the first induction dose	

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Subject				
Neutropenia	30			
Thrombocytopenia	6			
Febrile neutropenia	4			
Anemia	2			
Nephrotoxicity	2			
Infections	1			
Pulmonary toxicity	3			
Cardiotoxicity	1			
Urticaria	1			
Syncope	1			
Liver toxicity	1			
Ipomagnesemia	1			
Tumor lysis syndrome	1			
GI toxicity	0			
Neurotoxicity	1			
Edema	0			

Fatigue	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety evaluation Maintenance

End point title	Safety evaluation Maintenance

End point description:

Any grade III or higher toxicities will be recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (October 1, 2009).

End point type	Secondary

End point timeframe:

During maintenance therapy

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Subject				
Neutropenia	20			
Thrombocytopenia	2			
Febrile neutropenia	2			
Anemia	1			
Nephrotoxicity	0			
Infections	2			
Pulmonary toxicity	0			
Cardiotoxicity	0			
Urticaria	0			
Syncope	0			
Liver toxicity	0			
Ipomagnesemia	0			
Tumor lysis syndrome	0			
GI toxicity	1			
Neurotoxicity	1			
Edema	1			
Fatigue	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first induction dose or at any time during maintenance therapy (24 months).

Adverse event reporting additional description:

Any grade III or higher toxicities will be recorded and classified according to the definitions of NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (October 1, 2009).

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Single arm

Reporting group description:

R2-B treatment will be repeated for two cycles every 28 days, then patients will be evaluated for response; in case of CR, PR or SD, they will prosecute treatment for further two cycles. Patients after the end of the induction phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR and PR at the end of the induction phase, will continue therapy with a consolidation phase, that includes combination therapy with Lenalidomide and Rituximab (R2) every 28 days for 2 cycles.
Patients after the end of the consolidation phase who achieve less than PR will be treated according to best clinical practice but they will be included in the intention-to-treat population.
Patients in CR or PR at the end of the consolidation treatment will continue to a maintenance phase with Lenalidomide until disease progression or unacceptable toxicity up to 18 months, with 28-days cycles

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 42 (50.00%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oncologic complication			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung cancer			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mycoses fungoides			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Syncope			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Angioedema			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parenchymal lung disorders NEC			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 42 (92.86%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor lysis syndrome			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Cardiac disorders			
Cardiotoxicity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Nervous system disorders			

Neurotoxicity subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 3		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 32 / 42 (76.19%) 132 6 / 42 (14.29%) 12 4 / 42 (9.52%) 7 3 / 42 (7.14%) 3		
General disorders and administration site conditions Oedema subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1 1 / 42 (2.38%) 1		
Gastrointestinal disorders GI toxicity subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1		
Respiratory, thoracic and mediastinal disorders Pulmonary toxicity subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 3		
Hepatobiliary disorders Liver toxicity subjects affected / exposed occurrences (all)	 1 / 42 (2.38%) 1		
Skin and subcutaneous tissue disorders			

Urticaria subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Renal and urinary disorders Nephrotoxicity subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Infections and infestations Infections subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3		
Metabolism and nutrition disorders Hypomagnesemia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2013	1) Modification related to dose reduction of lenalidomide in patients with moderate renal insufficiency 2) Correction of refusals to adapt the correspondence between the text of the protocol and the appendices 3) Introduction to the side study (Cereblon evaluation) 4) Addendum to the information sheet / informed consent following the introduction of the side study (Cereblon evaluation) 5) The updated IB is sent.

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/28082342