Clinical trial results:
A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1 Infected Virologically Suppressed Adolescents

Summary

EudraCT number	2014-002673-11
Trial protocol	Outside EU/EEA
Global end of trial date	23 October 2017

Results information

Result version number	v1 (current)
This version publication date	23 March 2018
First version publication date	23 March 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-292-1515

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02276612
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, GileadClinicalTrials@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001460-PIP01-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2016
Global end of trial reached?	Yes
Global end of trial date	23 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-infected virologically suppressed adolescents 12 to < 18 years of age.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 52
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	60
EEA total number of subjects	0

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)	50
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in South Africa and the United States. The first participant was screened on 03 December 2014. The last study visit occurred on 23 October 2017.

Pre-assignment

Screening details:

68 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	E/C/F/TAF (12 - 17 Years of Age)

Arm description:

Participants 12 - 17 years of age received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants 12 - 17 years of age received E/C/F/TAF during the open-label extension phase.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Investigational medicinal product code	
Other name	E/C/F/TAF, Genvoya®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/10 mg fixed-dose combination (FDC) tablet administered once daily with food

Arm title	E/C/F/TAF (≥ 18 Years of Age)

Arm description:

Participants 18 years of age or older received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants ≥ 18 years of age received E/C/F/TAF during the open-label extension phase.

NOTE: Participants from Gilead Study GS-US-162-0112 were allowed to roll over into this Study GS-US-292-1515 even if they were 18 years or older at the time of screening.

Arm type	Experimental
Investigational medicinal product name	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
Investigational medicinal product code	
Other name	E/C/F/TAF, Genvoya®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150/150/200/10 mg FDC tablet administered once daily with food

Number of subjects in period 1	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)
Started	50	10
Completed	46	10
Not completed	4	0
Adverse event, serious fatal	1	-
Withdrew Consent	1	-
Pregnancy	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	E/C/F/TAF (12 - 17 Years of Age)
Reporting group description:	
Participants 12 - 17 years of age received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants 12 - 17 years of age received E/C/F/TAF during the open-label extension phase.	
Reporting group title	E/C/F/TAF (≥ 18 Years of Age)
Reporting group description:	
Participants 18 years of age or older received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants ≥ 18 years of age received E/C/F/TAF during the open-label extension phase. NOTE: Participants from Gilead Study GS-US-162-0112 were allowed to roll over into this Study GS-US-292-1515 even if they were 18 years or older at the time of screening.	

Reporting group values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)	Total
Number of subjects	50	10	60
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15	19	
standard deviation	± 1.6	± 1.2	-
Gender categorical Units: Subjects			
Female	32	3	35
Male	18	7	25
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	49	10	59
Race Units: Subjects			
Black	49	9	58
White	1	0	1
Other	0	1	1
HIV-1 RNA Category Units: Subjects			
< 50 copies/mL	49	9	58
≥ 50 copies/mL	1	1	2
CD4 Cell Count Units: cells/µL			
arithmetic mean	753	776	
standard deviation	± 222.5	± 179.9	-
CD4 Percentage Units: percentage			
arithmetic mean	34.3	35.9	

standard deviation	± 6.72	± 6.53	-

End points

End points reporting groups

Reporting group title	E/C/F/TAF (12 - 17 Years of Age)

Reporting group description:

Participants 12 - 17 years of age received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants 12 - 17 years of age received E/C/F/TAF during the open-label extension phase.

Reporting group title	E/C/F/TAF (≥ 18 Years of Age)

Reporting group description:

Participants 18 years of age or older received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants ≥ 18 years of age received E/C/F/TAF during the open-label extension phase.

NOTE: Participants from Gilead Study GS-US-162-0112 were allowed to roll over into this Study GS-US-292-1515 even if they were 18 years or older at the time of screening.

Primary: Incidence of Treatment-Emergent Serious Adverse Events

End point title	Incidence of Treatment-Emergent Serious Adverse Events[1]

End point description:

The percentage of participants experiencing any treatment-emergent serious adverse event was summarized. Safety Analysis Set included participants who were enrolled in the study and received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: percentage of participants				
number (not applicable)	4.0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Treatment-Emergent Adverse Events

End point title	Incidence of Treatment-Emergent Adverse Events[2]

End point description:

The percentage of participants experiencing any treatment-emergent adverse event was summarized. Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to Week 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical comparison was planned or performed.

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: percentage of participants				
number (not applicable)	92.0	100.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Plasma HIV-1 RNA Level < 50 Copies/mL at Week 24 (FDA-defined Snapshot Analysis)

End point title	Percentage of Participants With Plasma HIV-1 RNA Level < 50 Copies/mL at Week 24 (FDA-defined Snapshot Analysis)

End point description:

The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 24 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Full Analysis Set included participants who were enrolled in the study and received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Week 24

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: percentage of participants				
number (confidence interval 95%)	96.0 (86.3 to 99.5)	100.0 (69.2 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Plasma HIV-1 RNA Level < 50

Copies/mL at Week 48 (FDA-defined Snapshot Analysis)

End point title	Percentage of Participants With Plasma HIV-1 RNA Level < 50 Copies/mL at Week 48 (FDA-defined Snapshot Analysis)

End point description:

The percentage of participants achieving HIV-1 RNA < 50 copies/mL at Week 48 was analyzed using the snapshot algorithm, which defines a patient's virologic response status using only the viral load at the predefined time point within an allowed window of time, along with study drug discontinuation status. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: percentage of participants				
number (confidence interval 95%)	90.0 (78.2 to 96.7)	100.0 (69.2 to 100.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Cell Count at Week 24

End point title	Change From Baseline in CD4 Cell Count at Week 24

End point description:

Participants in the Full Analysis Set with on-treatment data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: cells/µL				
arithmetic mean (standard deviation)	-72 (± 189.8)	-85 (± 245.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Cell Count at Week 48

End point title	Change From Baseline in CD4 Cell Count at Week 48

End point description:

Participants in the Full Analysis Set with on-treatment data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	10		
Units: cells/µL				
arithmetic mean (standard deviation)	-43 (± 201.1)	-41 (± 143.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Percentage at Week 24

End point title	Change From Baseline in CD4 Percentage at Week 24

End point description:

Participants in the Full Analysis Set with on-treatment data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	10		
Units: percentage				
arithmetic mean (standard deviation)	-0.6 (± 5.46)	-0.6 (± 5.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CD4 Percentage at Week 48

End point title	Change From Baseline in CD4 Percentage at Week 48

End point description:

Participants in the Full Analysis Set with on-treatment data were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 48

End point values	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	10		
Units: percentage				
arithmetic mean (standard deviation)	-0.1 (± 3.95)	-1.1 (± 7.29)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 128 weeks plus 30 days

Adverse event reporting additional description:

Safety Analysis Set: participants who were enrolled in the study and received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	E/C/F/TAF (12 - 17 Years of Age)

Reporting group description:

Participants 12 - 17 years of age received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants 12 - 17 years of age received E/C/F/TAF during the open-label extension phase.

Reporting group title	E/C/F/TAF (≥ 18 Years of Age)

Reporting group description:

Participants 18 years of age or older received E/C/F/TAF for 48 weeks. Following completion of 48 weeks of treatment, eligible participants ≥ 18 years of age received E/C/F/TAF during the open-label extension phase.

NOTE: Participants from Gilead Study GS-US-162-0112 were allowed to roll over into this Study GS-US-292-1515 even if they were 18 years or older at the time of screening.

Serious adverse events	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 50 (2.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Electrocution			
subjects affected / exposed	1 / 50 (2.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 50 (2.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	E/C/F/TAF (12 - 17 Years of Age)	E/C/F/TAF (≥ 18 Years of Age)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 50 (84.00%)	10 / 10 (100.00%)	
Investigations			
Vitamin D decreased			
subjects affected / exposed	7 / 50 (14.00%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Bone density decreased			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			

Headache			
subjects affected / exposed	6 / 50 (12.00%)	2 / 10 (20.00%)	
occurrences (all)	6	2	
Dizziness			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Lymphadenopathy			
subjects affected / exposed	1 / 50 (2.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Axillary pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 50 (14.00%)	2 / 10 (20.00%)	
occurrences (all)	9	2	
Vomiting			
subjects affected / exposed	8 / 50 (16.00%)	1 / 10 (10.00%)	
occurrences (all)	8	2	

Abdominal pain upper			
subjects affected / exposed	3 / 50 (6.00%)	1 / 10 (10.00%)	
occurrences (all)	3	2	
Abdominal pain			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Constipation			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Anal fissure			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 50 (24.00%)	5 / 10 (50.00%)	
occurrences (all)	16	6	
Nasal obstruction			
subjects affected / exposed	3 / 50 (6.00%)	3 / 10 (30.00%)	
occurrences (all)	4	3	
Asthma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 50 (12.00%)	0 / 10 (0.00%)	
occurrences (all)	6	0	
Rash			
subjects affected / exposed	5 / 50 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	5	0	

Pruritus			
subjects affected / exposed	1 / 50 (2.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 50 (22.00%)	6 / 10 (60.00%)	
occurrences (all)	15	6	
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 50 (14.00%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Sinusitis			
subjects affected / exposed	3 / 50 (6.00%)	1 / 10 (10.00%)	
occurrences (all)	6	1	
Urinary tract infection			
subjects affected / exposed	4 / 50 (8.00%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Acarodermatitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Gastroenteritis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	5	1	
Lower respiratory tract infection			

subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Oral herpes			
subjects affected / exposed	1 / 50 (2.00%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Otitis media			
subjects affected / exposed	2 / 50 (4.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Herpes simplex			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Sinusitis bacterial			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 50 (8.00%)	1 / 10 (10.00%)	
occurrences (all)	4	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2016	• Updated total treatment duration from 96 weeks to 48 weeks to align with E.U. Pediatric Investigational Plan endpoints • Removed Week 72 and Week 96 visits as these visits are no longer applicable • Added Unscheduled Visit section to allow investigators to conduct additional study related safety visits when necessary • Clarified which assessments are to be completed at the extension phase of the study, and how often they are to be completed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported