Clinical trial results:
A study to assess near infrared laparoscopy with indocyanine green (ICG) for intraoperative lymphatic imaging and sentinel lymph node identification during standard surgical resection for colonic cancer

Summary

EudraCT number	2012-000424-18
Trial protocol	GB
Global end of trial date	26 October 2015

Results information

Result version number	v1 (current)
This version publication date	20 March 2016
First version publication date	20 March 2016

Trial information

Trial identification

Sponsor protocol code	ICTUC/32/2012

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	Room 215 Level 2, Medical School Building Norfolk Place, London, United Kingdom, W2 1PG
Public contact	Professor Robin Kennedy, St Marks Hospital - North West London Hospitals NHS Trust, 44 20 8235 4055, robin.kennedy@nhs.net
Scientific contact	Professor Robin Kennedy, St Marks Hospital - North West London Hospitals NHS Trust, 44 20 8235 4055, robin.kennedy@nhs.net

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	06 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2015
Global end of trial reached?	Yes
Global end of trial date	26 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish whether it is possible to identify the first order draining mesocolic lymph nodes (sentinel lymph node(s) (SLNs) in patients with suspected T1 and T2 colonic cancer, using ICG, a fluorescent mapping agent, and a laparoscopic near infrared imaging (NIR) system.

Protection of trial subjects:

During protocol development two main areas of risk were identified as requiring specific inclusion/exclusion criteria:

1. Risk of allergic (analphylactic or anaphylactoid) reaction which is deemed to be less than 1 in 10. This risk was highlighted in the protocol and all participants were asked about any prior exposure to the agent or reaction to iodine dyes and shellfish. In addition patient's notes were thoroughly reviewed by a member of the research team as part of the patient's eligibility assessment.
2. Adverse effects of pregnancy. A pregnancy test was performed in all women of childbearing potential as part of the assessment for eligibility and those who tested positive were excluded from the trial.

In addition a risk of colonic perforation (1/2000) related to the endoscopy procedure was highlighted. The procedure, was essential in order to inject the tracer agent and therefore the risk was minimized by effective bowel preparation and ensuring that this examination was performed by an experienced endoscopist. Finally it was stated the study will add 30 minutes to the total operative time. This was considered acceptable by the senior members of the investigative team and would have minimal risk to the patient.

An independent, combined Trial Steering Committee/Data Monitoring Committee was convened to oversee the trial.

Background therapy:

There were no protocol-specified background therapies. Concomitant medications could be prescribed at the treating physicians discretion, with the exception of prohibited medications described in the study protocol. Concomitant medications (and the reason for the medication) were recorded in the study database for the period 4-weeks prior to starting study treatment until the patient's last study visit.

Evidence for comparator: -

Actual start date of recruitment	26 June 2013
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	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	12
From 65 to 84 years	16
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study recruited all 30 patients in one UK site. This site opened to recruitment on 26/06/2016 and the first and last patient consent was on 30/08/2013 and 10/09/2015 respectively.

Pre-assignment

Screening details:

In total 145 patients were screened for the study, 111 were excluded on inclusion / exclusion criteria. The remaining 34 were approached to participate. Of those 34, 4 patients declined and 30 patients were consented to the study. Each patient consented met all inclusion and no exclusion criteria and was therefore enrolled onto the trial.

Period 1

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

Blinding implementation details:

Not Applicable

Arms

Arm title	Interventional Arm

Arm description:

There is only 1 arm in this study. All patients were in the interventional arm and received indocyanine green dye during their surgery so lymphatic imaging and sentinel lymph node identification could be performed as defined in the protocol.

Arm type	Experimental
Investigational medicinal product name	Indocyanine Green
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Submucosal use

Dosage and administration details:

5 ml of the mapping agent (ICG) were injected endoscopically into the submucosa in three / four points around the tumour

Number of subjects in period 1	Interventional Arm
Started	30
Completed	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	66		
standard deviation	± 12.4	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	16	16	
Ethnicity Units: Subjects			
White	19	19	
Mixed	0	0	
Asian	6	6	
Black	3	3	
Other	2	2	
Tumour Location Units: Subjects			
Caecum	7	7	
Ascending colon	4	4	
Hepatic flexure	1	1	
Transverse	1	1	
Splenic flexure	2	2	
Descending colon	1	1	
Sigmoid	11	11	
Rectosigmoid junction	3	3	
Operation Performed Units: Subjects			
Right hemicolectomy	12	12	

Transverse Colectomy	0	0	
High Anterior Resection	13	13	
Left Hemicolectomy	2	2	
Total Colectomy	1	1	
Extended Right Hemicolectomy	1	1	
Other	1	1	
Primary Tumour Size Units: Subjects			
T1	6	6	
T2	8	8	
T3	14	14	
T4	2	2	
Non-Malignant	0	0	
Nodal Status Units: Subjects			
N0	20	20	
N1	10	10	
N2	0	0	
N3	0	0	
NX	0	0	
Primary Cancer Units: Subjects			
Stage A	13	13	
Stage B	7	7	
Stage C1	10	10	
Stage C2	0	0	
Primary Tumour Grade Units: Subjects			
G1	4	4	
G2	24	24	
G3/4	2	2	
Unknown	0	0	
Body Mass Index Units: kg/m2			
arithmetic mean	27		
standard deviation	± 4	-	

Subject analysis sets

Subject analysis set title	T1/T2 Colon Cancer
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with stage T1/T2 colon cancer at baseline

Reporting group values	T1/T2 Colon Cancer		
Number of subjects	14		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	61.1		
standard deviation	± 10.4		
Gender categorical Units: Subjects			
Female	7		
Male	7		
Ethnicity Units: Subjects			
White	9		
Mixed	0		
Asian	4		
Black	1		
Other	0		
Tumour Location Units: Subjects			
Caecum	2		
Ascending colon	2		
Hepatic flexure	0		
Transverse	0		
Splenic flexure	1		
Descending colon	1		
Sigmoid	6		
Rectosigmoid junction	2		
Operation Performed Units: Subjects			
Right hemicolectomy	4		
Transverse Colectomy	0		
High Anterior Resection	8		
Left Hemicolectomy	1		
Total Colectomy	0		
Extended Right Hemicolectomy	0		
Other	1		
Primary Tumour Size Units: Subjects			
T1	6		
T2	8		
T3	0		
T4	0		
Non-Malignant	0		
Nodal Status Units: Subjects			
N0	12		

N1	2		
N2	0		
N3	0		
NX	0		
Primary Cancer Units: Subjects			
Stage A	12		
Stage B	0		
Stage C1	2		
Stage C2	0		
Primary Tumour Grade Units: Subjects			
G1	3		
G2	11		
G3/4	0		
Unknown	0		
Body Mass Index Units: kg/m2			
arithmetic mean	27.1		
standard deviation	± 4.7		

End points

End points reporting groups

Reporting group title	Interventional Arm

Reporting group description:

There is only 1 arm in this study. All patients were in the interventional arm and received indocyanine green dye during their surgery so lymphatic imaging and sentinel lymph node identification could be performed as defined in the protocol.

Subject analysis set title	T1/T2 Colon Cancer
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with stage T1/T2 colon cancer at baseline

Primary: Average number of sentinel lymph nodes identified for patients where sentinel lymph nodes were identified

End point title	Average number of sentinel lymph nodes identified for patients where sentinel lymph nodes were identified[1]

End point description:

End point type	Primary

End point timeframe:

Average number of sentinel lymph nodes identified for patients where sentinel lymph nodes were identified. This analysis was completed when the last patient had completed the trial.

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: Primary analysis was performed using a univariate methods. This method does not have an associated p-value. The EudraCT system would not allow statistical analysis details to be completed without entry of a p-value, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: Number of Sentinel Lymph Nodes				
arithmetic mean (standard deviation)				
Number of sentinel lymph nodes identified	2.9 (± 1.7)	2.6 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Average time to identification of lymphatic vessels in minutes

End point title	Average time to identification of lymphatic vessels in minutes[2]

End point description:

End point type	Primary

End point timeframe:

Average time to identification of lymphatic vessels in minutes. This analysis was performed when the

last patient had completed the trial.

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: Primary analysis was performed using a univariate methods. This method does not have an associated p-value. The EudraCT system would not allow statistical analysis details to be completed without entry of a p-value, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: Minutes				
arithmetic mean (standard deviation)				
Time to Identification (Lymphatic Vessels)	5.4 (± 2.6)	5.4 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Average time to Identification of lymph nodes

End point title	Average time to Identification of lymph nodes[3]

End point description:

End point type	Primary

End point timeframe:

Average time to Identification of lymph nodes. This analysis was completed when the last patient completed the trial.

Notes:

[3] - 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: Primary analysis was performed using a univariate methods. This method does not have an associated p-value. The EudraCT system would not allow statistical analysis details to be completed without entry of a p-value, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: Minutes				
arithmetic mean (standard deviation)				
Time to identification (lymph nodes)	7.4 (± 3.5)	7.4 (± 2.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with aberrant nodal drainage.

End point title	Number of patients with aberrant nodal drainage.[4]

End point description:

End point type	Primary

End point timeframe:

Number of patients with aberrant nodal drainage. This analysis was performed when the last patient had completed the trial.

Notes:

[4] - 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: Primary analysis was performed using a univariate methods. This method does not have an associated p-value. The EudraCT system would not allow statistical analysis details to be completed without entry of a p-value, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: Number of Patients				
number (confidence interval 95%)				
Aberrant nodal drainage	0 (0 to 12)	0 (0 to 23)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients in which sentinel lymph nodes were identified

End point title	Number of patients in which sentinel lymph nodes were identified[5]

End point description:

End point type	Primary

End point timeframe:

Number of patients in which sentinel lymph nodes were identified as assessed when the last patient had completed the study.

Notes:

[5] - 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: Primary analysis was performed using a univariate methods. This method does not have an associated p-value. The EudraCT system would not allow statistical analysis details to be completed without entry of a p-value, however, this does not exist for this data set. Therefore we are unable to add statistical analysis details due to operational errors with the database.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: percent				
number (confidence interval 95%)				
Sentinel Lymph Nodes Identified	90 (73 to 98)	93 (66 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity of sentinel node findings

End point title	Sensitivity of sentinel node findings

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed after the last patient had completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[6]	14[7]		
Units: percent				
number (confidence interval 95%)				
Sensitivity of sentinel node findings	30 (7 to 65)	0 (0 to 84)		

Notes:

[6] - Diagnostic test results include 3 patients with no SLNs identified. Patients assumed to be negative.

[7] - Diagnostic test results include 1 patient with no SLNs identified. Patient assumed to be negative.

Statistical analyses

No statistical analyses for this end point

Secondary: Specificity of sentinel node findings

End point title	Specificity of sentinel node findings

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed when the last patient completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[8]	14[9]		
Units: percent				
number (confidence interval 95%)				
specificity of sentinel node findings	100 (83 to 100)	100 (74 to 100)		

Notes:

[8] - Diagnostic test results include 3 patients with no SLNs identified. Patients assumed to be negative.

[9] - Diagnostic test results include 1 patient with no SLNs identified. Patient assumed to be negative.

Statistical analyses

No statistical analyses for this end point

Secondary: Positive predictive value of sentinel node findings

End point title	Positive predictive value of sentinel node findings

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed when the last patient completed the study.

End point values	Interventional Arm			
Subject group type	Reporting group			
Number of subjects analysed	30[10]			
Units: percent				
number (confidence interval 95%)				
positive predictive value of sentinel node finding	100 (29 to 100)			

Notes:

[10] - Diagnostic test include 3 patients with no SLN identified. Patients assumed negative

Statistical analyses

No statistical analyses for this end point

Secondary: Negative predictive value of sentinel node findings

End point title	Negative predictive value of sentinel node findings

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed when the last patient had completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[11]	14[12]		
Units: percent				
number (confidence interval 95%)				
Negative predictive value of sentinel node finding	74 (54 to 89)	86 (57 to 98)		

Notes:

[11] - Diagnostic test results include 3 patients with no SLNs identified. Patients assumed to be negative.

[12] - Diagnostic test results include 1 patient with no SLNs identified. Patient assumed to be negative.

Statistical analyses

No statistical analyses for this end point

Secondary: Accuracy of sentinel node findings

End point title	Accuracy of sentinel node findings

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed when the last patient has completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30[13]	14[14]		
Units: percent				
number (confidence interval 95%)				
Accuracy of sentinel node findings	77 (58 to 90)	86 (57 to 98)		

Notes:

[13] - Diagnostic test results include 3 patients with no SLNs identified. Patients assumed to be negative.

[14] - Diagnostic test results include 1 patient with no SLNs identified. Patient assumed to be negative.

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with aberrant sentinel nodes

End point title	Patients with aberrant sentinel nodes

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed after the last patient had completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: percent				
number (confidence interval 95%)				
Patients with aberrant sentinel nodes	0 (0 to 12)	0 (0 to 23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with positive aberrant nodes

End point title	Patients with positive aberrant nodes

End point description:

End point type	Secondary

End point timeframe:

This analysis was performed after the last patient had completed the study.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: percent				
number (confidence interval 95%)				
Patient with positive aberrant nodes	0 (0 to 12)	0 (0 to 23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of lymph nodes identified per patient

End point title	Number of lymph nodes identified per patient

End point description:

End point type	Secondary

End point timeframe:

Average number of lymph nodes identified for patients. This analysis was completed when the last patient had completed the trial.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: Number of Lymph Nodes				
arithmetic mean (standard deviation)				
Number of lymph nodes identified per patient	33.3 (± 14.3)	31.1 (± 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with positive nodes

End point title	Number of patients with positive nodes

End point description:

End point type	Secondary

End point timeframe:

Percentage of patients with positive nodes. This analysis was completed when the last patient had completed the trial.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: percent				
number (not applicable)				
Number of patients with positive nodes	33	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with positive sentinel nodes

End point title	Number of patients with positive sentinel nodes

End point description:

End point type	Secondary

End point timeframe:

Percentage of patients with positive sentinel nodes. This analysis was completed when the last patient

had completed the trial.

End point values	Interventional Arm	T1/T2 Colon Cancer		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	14		
Units: percent				
number (not applicable)				
Number of patients with positive sentinel nodes	10	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from the time a patient signed informed consent until the end of followup. AEs were followed-up according to local practice until the event has stabilised or resolved, or until the last follow-up visit, whichever was sooner

Adverse event reporting additional description:

AEs were reviewed at every patient visit.
AEs we assessed for severity (NCI CTCAE v4.03) and causality by the local PI; the CI provided an assessment for SAEs. All AEs were recorded in the study EDC system.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Interventional Arm

Reporting group description:

All patients that received at least one dose of the IMP

Serious adverse events	Interventional Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Interventional Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Postoperative ileus			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

Wound Pain subjects affected / exposed occurrences (all)	29 / 30 (96.67%) 29		
Vascular disorders Blood pressure decreased subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all) Paroxysmal Atrial Fibrillation subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Nervous system disorders Tremor subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
General disorders and administration site conditions Febrile Reaction subjects affected / exposed occurrences (all) Rigors subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Abdominal distension	1 / 30 (3.33%) 1		

subjects affected / exposed occurrences (all) Epigastric discomfort subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all) Ileus subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Bloating subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1 4 / 30 (13.33%) 4 12 / 30 (40.00%) 12 3 / 30 (10.00%) 3 2 / 30 (6.67%) 2		
Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		
Musculoskeletal and connective tissue disorders Groin pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		

Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported