



## Clinical trial results:

### A Phase II study in patients with locally advanced pancreatic carcinoma: ARC-II – Akt-inhibition by Nelfinavir plus chemoradiation with gemcitabine and cisplatin

#### Summary

EudraCT number	2008-006302-42
Trial protocol	GB
Global end of trial date	27 May 2015

#### Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	08 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	309/H0604/36
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##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	Clinical Trials & Research Governance, University Oxford
Sponsor organisation address	Churchill Hospital Headington, Oxford, United Kingdom, OX3 7LE
Public contact	Somnath Mukherjee, Early Phase Research Hub (ARC II), 44 1865235302, earlyphasehub@oncology.ox.ac.uk
Scientific contact	Somnath Mukherjee, Early Phase Research Hub (ARC II), 44 1865235302, earlyphasehub@oncology.ox.ac.uk

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	05 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2015
Global end of trial reached?	Yes
Global end of trial date	27 May 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess if the addition of nelfinavir to gemcitabine and cisplatin chemoradiotherapy improves survival and merits further study.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. Together, these regulations implement the ethical principles of the Declaration of Helsinki (2008) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directives 001/20/EC (Clinical Trials) and 2005/28/EC (GCP). Standard phase II cancer clinical trial methodology using an agent with a very well known toxicity profile in an unlicensed indication. Subjects were monitored closely for toxicity.

Background therapy:

Gemcitabine and cisplatin chemoradiotherapy (CRT).

Radiotherapy is delivered daily (Monday to Friday). The total dose is 50.4 Gy in 28# (1.8Gy/#) to the elective regional lymph nodes and 59.4 Gy in 33# (1.8Gy/#) to the primary tumour. The first day of radiotherapy should be a Monday (day 1) if feasible but flexibility of  $\pm 1$  day is allowed.

Gemcitabine is administered IV at 300 mg/m<sup>2</sup> BSA on days 2, 9, 23, and 30 (corresponding to Tuesday of the 1st, 2nd, 4th and 5th week of radiotherapy) where feasible but flexibility of  $\pm 1$  day is allowed.

Cisplatin is administered IV at 30 mg/m<sup>2</sup> BSA on days 2, 9, 23, and 30 (corresponding to Tuesday of the 1st, 2nd, 4th and 5th week of radiotherapy) where feasible but flexibility of  $\pm 1$  day is allowed.

Radiotherapy should be given within one hour of completing the cisplatin infusion.

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 December 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

<b>Subjects enrolled per age group</b>	
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	12
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Trial recruited from a single UK centre between 02Dec2009 and 15 Jul2014. First patient was recruited 18Jan2010.

### Pre-assignment

Screening details:

In total 39 patients were screened. Sixteen (16) were excluded. Of these 10 were not eligible and six declined.

### Period 1

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

### Arms

Arm title	Overall trial
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Arm description:

Overall trial (Single arm)

Arm type	Experimental
Investigational medicinal product name	Nelfinavir mesotheliate
Investigational medicinal product code	
Other name	VIRACEPT®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally at a dose of 1250mg bd on Days -8 to 45 (this corresponds to five 250mg tablets in the morning and five 250mg tablets in the evening)

Number of subjects in period 1	Overall trial
Started	23
Received study intervention	23
Completed 12 month follow-up	22
Completed	22
Not completed	1
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Trial
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Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	23	23	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	13	13	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	13	13	
Karnofsky Performance Status			
Units: Subjects			
>80	15	15	
70-80	7	7	
Not recorded	1	1	

## End points

### End points reporting groups

Reporting group title	Overall trial
Reporting group description:	
Overall trial (Single arm)	

### Primary: Proportion of subjects surviving to 12 months after trial entry

End point title	Proportion of subjects surviving to 12 months after trial entry <sup>[1]</sup>
End point description:	

End point type	Primary
End point timeframe:	
12 months after trial entry	

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: This is a single arm, non-comparative study.

EudraCT – Results Webinar 27 January 2016 advises:

Q2: unable to upload stats for one analysis group when this will be implemented and what to do meantime?

A2: if the trial includes only one arm or one reporting group, results can be prepared and endpoints can be reported upon for this reporting group/arm. The statistical analysis being optional.

<b>End point values</b>	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Patients				
number (confidence interval 90%)				
Alive at 12 months	73.4 (54.5 to 85.5)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival at 12 months

End point title	Progression Free Survival at 12 months
End point description:	

End point type	Secondary
End point timeframe:	
12 months after entry on trial	

<b>End point values</b>	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	19 <sup>[2]</sup>			
Units: Subjects				
Progression free	12			
Progressive disease	7			

Notes:

[2] - None evaluable: 2 died prior to 12 months, 1 did not complete treatment, 1 died at end of treatment.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Resectability after primary non-resectability

End point title	Resectability after primary non-resectability
End point description:	Result of restaging investigations following treatment with nelfinavir and chemo-radiotherapy.
End point type	Secondary
End point timeframe:	6-8 weeks after completion of chemo-radiotherapy

<b>End point values</b>	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[3]</sup>			
Units: Subjects				
Resectable	2			
Not resectable	19			

Notes:

[3] - 2 died before restaging

### Statistical analyses

No statistical analyses for this end point

### Secondary: Site of treatment failure/ first progression

End point title	Site of treatment failure/ first progression
End point description:	Loco-regional progression within radiotherapy treatment field vs distant progression outside the treatment field
End point type	Secondary
End point timeframe:	Overall time to progression

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: subjects				
Loco-regional progression	4			
Distant progression	15			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective response (RECIST)

End point title	Objective response (RECIST)
End point description:	
End point type	Secondary
End point timeframe:	
Restaging 6-8 weeks after end of chemo-radiotherapy	

End point values	Overall trial			
Subject group type	Reporting group			
Number of subjects analysed	21 <sup>[4]</sup>			
Units: subjects				
Complete response	0			
Partial response	5			
Stable disease	10			
Progressive disease	6			

Notes:

[4] - Two died before restaging

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of treatment to 28 days post end of treatment

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description:

Overall trial (Single arm)

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 23 (65.22%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	0		
Investigations			
Decreased lymphocytes			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Increased bilirubin			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
fall- cut above right eye and graze on the right cheek			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusion of unknown cause			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Extravasation of F-MISO Dye			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea	Additional description: Probably related to radiotherapy		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	4 / 23 (17.39%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Rectal bleeding			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 23 (95.65%)		
Investigations			
Decreased CD4 lymphocytes			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Decreased lymphocytes			
subjects affected / exposed	19 / 23 (82.61%)		
occurrences (all)	48		
Decreased neutrophils			
subjects affected / exposed	8 / 23 (34.78%)		
occurrences (all)	14		
Decreased white blood cells			
subjects affected / exposed	8 / 23 (34.78%)		
occurrences (all)	15		
Elevated alkaline Phosphatase			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	5		
Increased ALT			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	8		
Increased AST			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	2		
Increased bilirubin			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	7		
Increased GGT			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Abnormal LFTs			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Thrombocytopenia			

subjects affected / exposed occurrences (all)  Weight loss diet subjects affected / exposed occurrences (all)	16 / 23 (69.57%)  26  2 / 23 (8.70%)  2		
Injury, poisoning and procedural complications Bleeding PICC line exit subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		
Vascular disorders Splenic vein thrombosis subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		
Nervous system disorders Anxiety and confusion subjects affected / exposed occurrences (all)  Drowsiness subjects affected / exposed occurrences (all)  Dysarthria subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1  3 / 23 (13.04%)  3  1 / 23 (4.35%)  1		
Dysgeusia	Additional description: Loss of taste		
subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		
Headache subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		
Restless legs syndrome subjects affected / exposed occurrences (all)	1 / 23 (4.35%)  1		

Seizure			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 23 (52.17%)		
occurrences (all)	14		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 23 (69.57%)		
occurrences (all)	35		
Fever			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Flu-like symptoms			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Eye disorders			
Blurred vision			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 23 (21.74%)		
occurrences (all)	7		
Anorexia			

subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	16 / 23 (69.57%)		
occurrences (all)	30		
Distended abdomen			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Faecal incontinence			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastro-oesophageal reflux			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Haematemesis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	18 / 23 (78.26%)		
occurrences (all)	37		
Pancreatic enzymes decreased	Additional description: Steatorrhea		

subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	11 / 23 (47.83%)		
occurrences (all)	28		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Skin rash			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Sepsis	Additional description: One Neutropenic sepsis and the other pneumonia		
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Hypoglycaemia	Additional description: Hypoglycemic episode		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	6 / 23 (26.09%)		
occurrences (all)	9		





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2010	<p>Extensive revision of protocol formatting and wording throughout to improve brevity and clarity without changing the original clinical or scientific intent of the authors.</p> <p>Addition of the Oxford University Oncology Clinical Trials Office (OCTO) for coordination of the multicentre trial .</p> <p>Intention to follow patients for overall survival added as a secondary endpoint</p> <p>intention to look for a correlation of response in imaging and response in histopathology in resected patients added as a new secondary endpoint</p> <p>Clarification that examining the effect of nelfinavir treatment on phospho-Akt expression is an exploratory objective.</p> <p>Addition of Radiotherapy Quality Assurance.</p> <p>For safety reasons random glucose will be monitored in blood tests taken while patient is receiving nelfinavir as there is a small increased risk of diabetes.</p> <p>Research blood samples increased from 30ml at 2 time points to a total 70ml per patient to 35ml on 7 occasions (screen, wks 2, 3, 4, 5,6,7,) to a total of 245ml per patient;</p> <p>Reduced duration of formal trial follow-up visits to 12 months post CRT (patients will be seen in trial clinics for ~14 months).</p> <p>Added clarification of intent to follow-up all patients longer term as necessary to record progression free survival and overall survival;</p> <p>Addition of optional collection of surplus formalin fixed tissue from routine diagnostic biopsy and surgery.</p> <p>Classify routine, planned hospital admissions for supportive care or social reasons as SAEs which do not require immediate reporting.</p> <p>Require reports to be submitted in the case of pregnancies (in a trial subject or subject's partner).</p> <p>The 'end of trial' is defined as 18 months after enrolment of the last patient into the trial.</p> <p>Increase participating Centres</p> <p>New information on contra-indications given in current SmPC for nelfinavir (Viricept) dated 08Feb10 incorporated into Protocol</p> <p>Changes to patient information sheet and GP letter</p>
18 December 2012	<p>Change of Chief Investigator</p> <p>Addition of a functional imaging cohort and associated secondary and exploratory endpoint measures</p> <p>Additional research blood sampling at functional imaging timepoints</p> <p>Obtain pre-screening consent for 18F-FDG-PET scan to exclude distant metastases prior to main trial screening</p> <p>Increase duration of nelfinavir induction from 3 to 9 days prior to start of background chemo-radiotherapy</p> <p>Minor administrative changes</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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16 August 2011	<p>Temporary halt to recruitment to ARC II for administrative reasons.</p> <p>Recruitment put on hold pending production, submission and approval of a substantial amendment. That will enable the study to re-open as a single centre (Oxford only) trial that incorporates a functional imaging component. The number of participants will be reduced and primary end point of the trial will be amended in light of recent new studies on a similar theme.</p> <p>2. To facilitate an agreed transfer of responsibility for coordination from the Oxford Oncology Clinical Trials Office (OCTO) which specialises in the conduct of multicentre trials to the Early Phase Hub, an administratively separate team within Oncology which specialises in smaller translational trials.</p> <p>3. Making the trial single centre enables the integration of a functional imaging component that will enhance the scientific importance of the study. We wish to maximise the number of patients recruited into the imaging cohort.</p> <p>4. The trial has recruited well in Oxford to date and remains viable as a single centre study. There is considerable interest and support elsewhere and It is hoped that ARC II will lead into to a nationally adopted larger scale study. Hence the scientific and clinical importance of the protocol is not affected.</p> <p>5. The Sponsor and Early Phase Hub agreed to put recruitment on hold in order to ensure there is an orderly transfer from OCTO. The temporary halt will allow time for the protocol amendment to be written and a backlog of monitoring and data collection cleared.</p> <p>6. An initial monitoring visit conducted by the Sponsor (10th August 2011) to assess the current situation at the study site did not raise any major concerns over the safety and rights of participants, the overall risk benefit assessment of the investigational medicinal product or the scientific value of the trial.</p>	13 January 2012
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Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study had several shortcomings. It was not randomised, recruitment was difficult resulting in a lack of power to address the primary endpoint. So the promising outcome from the trial needs to be interpreted with caution.

Notes:

## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27117177>