Clinical trial results:
Antiplatelet treatment in patients with diabetes mellitus: is there a difference between aspirin, clopidogrel and prasugrel

Summary

EudraCT number	2009-011907-22
Trial protocol	GB
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	09 May 2020
First version publication date	09 May 2020
Summary attachment (see zip file)	Antiplatelet in Diabetes final report (2020.03.10 (rcvd)_Prasugrel-2020.pdf)

Trial information

Trial identification

Sponsor protocol code	ED09/8912

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Worsley Building, Leeds, United Kingdom, LS2 9JT
Public contact	Dr Ramzi Ajjan, University of Leeds, R.Ajjan@leeds.ac.uk
Scientific contact	Dr Ramzi Ajjan, University of Leeds, R.Ajjan@leeds.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	31 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the biochemical efficacy of Aspirin, Clopidegrel and Prasugrel in subjects with type 2 diabetes using a dual approach that investigates both platelet function and clot structure/fibrinolysis

Protection of trial subjects:

This clinical trial, which involves the use of a medicinal product has been designed and will be run in accordance with the Principles of GCP and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.. The right of any individual to refuse consent without giving reasons will be respected. Furthermore, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. Each participant will be involved in the study for a maximum of 10 weeks. Patients will need to attend on 5 occasions. Additional visits will be arranged at subject request or if this is deemed clinically necessary. AEs will be collected for all patients and will be evaluated for duration and intensity according to the NCRI Common Toxicity Criteria.

Background therapy:

Diabetes is associated with increased risk of vascular disease, including heart attack and strokes 1. People with diabetes also have a worse short and long term prognosis following a heart attack with a higher death rate, when compared to non-diabetics 2. Antiplatelet therapy is an established management strategy for secondary prevention from cardiovascular events in people with diabetes, although the role of this agent in primary prevention in these subjects remains unclear as the evidence is both limited and inconclusive. Aspirin and clopidogrel are the two main antiplatelet agents currently in use, and they differ in their mechanism of action. Aspirin affects platelet function by inhibiting an enzyme called cyclo-oxygenase 1, which is important for the production of proteins involved in platelet activation. Furthermore, aspirin has a direct effect on the structure of blood clots, making them easier to breakdown (lyse) 3. Clopidogrel also inhibits the function of platelets but uses a different pathway by directly inhibiting platelet function through its action on a special receptor called P2Y12. In contrast to aspirin, the effects of this agent on clot structure and function are unknown. Prasugrel, a new antiplatelet agent that has recently obtained marketing authorization and that is now marketed in the UK, has a similar mode of action compared with clopidogrel but seems to have a superior clinical efficacy 4, which is probably related to greater and more consistent inhibition of platelet activation 5.

Evidence for comparator: -	
Actual start date of recruitment	29 May 2010
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: 56

Worldwide total number of subjects	56
EEA total number of subjects	56

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)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were eligible to participate if they were aged 18–75 years, already on treatment with aspirin 75 mg once-daily (OD) and able to give informed consent.

Pre-assignment

Screening details:

Patients will be recruited in the diabetes centre at Leeds Teaching Hospitals Trust and specialist cardiovascular/diabetes clinics. A verbal explanation of the trial and an Information Sheet will be provided by Dr Ajjan for the subject to consider. This will include detailed information about the rationale, design and personal implications

Period 1

Period 1 title	Main Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg

Arm description:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. This arm then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg
OD for 28 days.

Arm type	Experimental
Investigational medicinal product name	Aspirin 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Investigational medicinal product name	Clopidogrel 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Investigational medicinal product name	Prasugrel 10mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Arm title	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg

Arm description:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. This arm thenreceived prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 days, in an alternate sequence to Arm 1.

Arm type	Experimental
Investigational medicinal product name	Aspirin 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Investigational medicinal product name	Clopidogrel 75mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Investigational medicinal product name	Prasugrel 10mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. One half then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg OD for 28 days, whilst the other half received prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 Days

Number of subjects in period 1	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg
Started	28	28
Completed	28	28

Baseline characteristics

Reporting groups

Reporting group title	Main Trial Period

Reporting group description: -

Reporting group values	Main Trial Period	Total	
Number of subjects	56	56	
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	60.7		
full range (min-max)	46 to 73	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	47	47	

End points

End points reporting groups

Reporting group title	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg

Reporting group description:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. This arm then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg
OD for 28 days.

Reporting group title	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg

Reporting group description:

All patients continued aspirin 75 mg OD for an
initial lead-in period of 14 days. This arm thenreceived prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 days, in an alternate sequence to Arm 1.

Primary: Prasugrel Maximum platelet aggregation response

End point title	Prasugrel Maximum platelet aggregation response[1]

End point description:

Please note, maximum platelet aggregation response is recorded on the system for the each treatment. not via each arm in the study, as treatment was identical, just at different time points. This is to accommodate the unusual design of the study. For more information on the end point data, please see the attached publication.

End point type	Primary

End point timeframe:

please see attached publication for the details regarding periods of assesment

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: Please see attached publication for details of all statistical analysis

End point values	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: 20µmol/L				
arithmetic mean (standard deviation)	34.1 (± 14.1)	34.1 (± 14.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Aspirin Maximum platelet aggregation response

End point title	Aspirin Maximum platelet aggregation response[2]

End point description:

Please note, maximum platelet aggregation response is recorded on the system for the each treatment. not via each arm in the study, as treatment was identical, just at different time points. This is to accommodate the unusual design of the study. For more information on the end point data, please see the attached publication.

End point type	Primary

End point timeframe:

Please see attached publication for time frame details

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: Please see attached publication for details of all statistical analysis

End point values	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: 20µmol/L				
arithmetic mean (standard deviation)	77.6 (± 8.4)	77.6 (± 8.4)		

Statistical analyses

No statistical analyses for this end point

Primary: Clopidogrel Maximum platelet aggregation response

End point title	Clopidogrel Maximum platelet aggregation response[3]

End point description:

Please note, maximum platelet aggregation response is recorded on the system for the each treatment, not via each arm in the study, as treatment was identical, just at different time points. This is to accommodate the unusual design of the study. For more information on the end point data, please see the attached publication.

End point type	Primary

End point timeframe:

Please see attached publication for all timeframe details

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: Please see attached publication for details of all statistical analysis

End point values	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: 20µmol/L				
arithmetic mean (standard deviation)	57.7 (± 17.6)	57.7 (± 17.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs will be collected for all patients at all visits, and will be evaluated for duration and intensity according to the NCRI Common Toxicity Criteria.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg

Reporting group description:

All patients continued aspirin 75 mg OD for an initial lead-in period of 14 days. This arm then received clopidogrel 75 mg OD for 28 days then prasugrel 10 mg
OD for 28 days.

Reporting group title	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg

Reporting group description:

All patients continued aspirin 75 mg OD for an
initial lead-in period of 14 days. This arm thenreceived prasugrel 10 mg OD for 28 days followed by clopidogrel 75 mg OD for 28 days, in an alternate sequence to Arm 1.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see the attached final publication for details of Non-serious adverse events

Serious adverse events	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Right Toe Ulcer			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Dizzyness			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (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: 0 %

Non-serious adverse events	Aspirin 75mg, Clopidogrel 75mg, Prasugrel 10mg	Aspirin 75mg, Prasugrel 10mg, Clopidogrel 75mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 28 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2010	PIS amended to v4.0, to include the contact details of a new research nurse joining the research team
22 July 2011	Protocol & PIS amended to versions 4.0 & 5.0.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported