Clinical trial results:
MICROVASCULAR AND ANTIINFLAMMATORY EFFECTS OF RIVAROXABAN COMPARED TO LOW DOSE ASPIRIN IN TYPE 2 DIABETIC PATIENTS WITH VERY HIGH CARDIOVASCULAR RISK AND SUBCLINICAL INFLAMMATION

Summary

EudraCT number	2014-001305-41
Trial protocol	DE
Global end of trial date	12 December 2018

Results information

Result version number	v1 (current)
This version publication date	04 June 2022
First version publication date	04 June 2022

Trial information

Trial identification

Sponsor protocol code	MicroVasc-DIVA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02164578
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GWT-TUD GmbH
Sponsor organisation address	Freiberger Str. 33, Dresden, Germany, 01067
Public contact	Medical Consulting, GWT-TUD GmbH, 0049 35125933100, medical.consulting@g-wt.de
Scientific contact	Medical Consulting, GWT-TUD GmbH, 0049 35125933100, medical.consulting@g-wt.de

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	11 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2018
Global end of trial reached?	Yes
Global end of trial date	12 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Difference of change of forearm blood flow with venous occlusion plethysmography at baseline and after forearm ischemia after 20 weeks treatment between rivaroxoban and aspirin therapy.
Additionally the difference of arterial stiffness after the end of the extension study (week 52) between rivaroxoban and aspirin therapy will be evaluated.

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailes in the Declaration of Helsinki. The study waas also carried out in keeping with applicable local law(s) and regulation(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2015
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	Germany: 179
Worldwide total number of subjects	179
EEA total number of subjects	179

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)	92
From 65 to 84 years	87

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 14th Apr 2015 through 21st Dec 2017, a total of 239 patients were screened at 4 study sites in Germany. Of them, 60 patients did not meet the eligibility criteria. 188 patients were planned to enrol and 80 patients of them should included in the extension period of the study.

Pre-assignment

Screening details:

179 patients were randomized to one of the two treatment groups, 89 to receive rivaroxaban and 90 to receive acetylsalicylic acid (ASA). In total, 73 patients were included in the extension period, 37 of them received rivaroxaban and 36 received ASA.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban

Arm description:

The arm with 5 mg b.i.d. Rivaroxaban consisted of a treatment period of 20 weeks and of an extension period of additional 32 weeks. From 72 patients 37 patients were included in the extension phase.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received Rivaroxaban 5 mg b.i.d. for the duration of 20 weeks.
Additionally, 37 patients of the study population continued to receive the Rivaroxaban 5 mg b.i.d. for further 32 weeks (extension treatment).

Arm title	Aspirin

Arm description:

The arm with 100 mg q.d. Aspirin consisted of a treatment period of 20 weeks and of an extension period of additional 32 weeks. From 79 patients 36 patients were included in the extension phase.

Arm type	Active comparator
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received treatment with Aspirin 100 mg q.d. for the duration of 20 weeks.
Additionally, 36 patients of the study population continued to receive the Aspirin 100 mg q.d. for further 32 weeks (extension treatment).

Number of subjects in period 1	Rivaroxaban	Aspirin
Started	89	90
Completed	72	79
Not completed	17	11
Consent withdrawn by subject	3	3
Physician decision	1	-
Adverse event, non-fatal	13	6
Protocol deviation	-	2

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	179	179	
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)	92	92	
From 65-84 years	87	87	
85 years and over	0	0	
Age continuous Units: years			
median	65		
standard deviation	± 7.11	-	
Gender categorical Units: Subjects			
Female	95	95	
Male	84	84	

End points

End points reporting groups

Reporting group title	Rivaroxaban
Reporting group description:	
The arm with 5 mg b.i.d. Rivaroxaban consisted of a treatment period of 20 weeks and of an extension period of additional 32 weeks. From 72 patients 37 patients were included in the extension phase.	
Reporting group title	Aspirin
Reporting group description:	
The arm with 100 mg q.d. Aspirin consisted of a treatment period of 20 weeks and of an extension period of additional 32 weeks. From 79 patients 36 patients were included in the extension phase.	

Primary: Change in Post-ischemic Forearm Blood Flow

End point title	Change in Post-ischemic Forearm Blood Flow
End point description:	
Change of maximal postischemic forearm blood flow during reactive hyperaemia after 5 min of forearm ischemia (FBF max. ml/100ml).	
End point type	Primary
End point timeframe:	
week 20	

End point values	Rivaroxaban	Aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	84		
Units: FBF (max)				
arithmetic mean (standard deviation)	3.60 (± 4.69)	1.00 (± 5.27)		

Statistical analyses

Statistical analysis title	Efficacy analysis
Comparison groups	Rivaroxaban v Aspirin
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Primary: Change in pulse wave velocity

End point title	Change in pulse wave velocity
End point description:	

End point type	Primary
End point timeframe: week 52	

End point values	Rivaroxaban	Aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: m/s				
arithmetic mean (standard deviation)	0.24 (± 0.62)	0.51 (± 0.57)		

Statistical analyses

Statistical analysis title	Efficacy analysis
Comparison groups	Rivaroxaban v Aspirin
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.07
Method	ANCOVA

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

from day 0 to week 52

Adverse event reporting additional description:

Adverse events and serious adverse events were collected from first intake of study medication and then at each visit until the end of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Rivaroxaban
Reporting group description: -	
Reporting group title	Aspirin
Reporting group description: -	

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: Overall, 125 out of the 179 patients (69.8%) in the SAF experienced at least one AE, 63 (70.8%) in the rivaroxaban arm and 62 (68.9%) in the ASA arm. Most of the AEs were of mild (37.0%) or moderate (52.6%) intensity. 34 AEs (10.4%) of severe intensity were documented, 22 events in the rivaroxaban arm and 12 events in the ASA arm. In total, 25.1% of the AEs were assessed as possibly or likely related to the study medication, 29.6% in the rivaroxaban arm and 19.6% in the aspirin arm.

Serious adverse events	Rivaroxaban	Aspirin	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 89 (4.49%)	6 / 90 (6.67%)	
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)			
Cerebrovascular accident			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leiomyoma			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Foot fracture			

subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 89 (0.00%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint arthroplasty			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (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			
Chest pain			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	Rivaroxaban	Aspirin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2015	Version 5.0 dated 01 Jul 2015: change in inclusion criteria, introduction of additional lab parameters; extension of screening phase
04 August 2016	Version 6.0 dated 07 Jul 2016: introduction of extension phase

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported