

Safety and effectiveness of WF10 for diabetes-related blood vessel diseases

Submission date 11/08/2022	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered
		<input type="checkbox"/> Protocol
Registration date 12/08/2022	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
Last Edited 12/08/2022	Condition category Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

Plain English summary of protocol

Background and study aims

WF10 is a chlorite-based drug solution applied via intravenous infusion (into a vein). The drug is already registered in Thailand for the co-treatment of diabetic foot ulcers (DFUs), a medical complication in diabetic patients resulting from diabetes-related blood vessel diseases. The study aims to confirm that the drug reduces high hemoglobin A1c (HbA1c) values in diabetic patients by restoring red blood cell (RBC) homeostasis (stability). Furthermore, the removal of highly glycated “sick” RBCs from the blood should also lead to improvement of vasculopathy (i.e. blood vessel disease) in the patients with the result of reduced inflammation and improved wound healing in the patients. The study further aims to show that the described drug activity also leads to the reduction of advanced glycation end products (AGEs). The latter are compounds that are formed in diabetic patients and most likely contribute to the development of diabetic complications.

Who can participate?

Patients aged 18 to 80 years with high HbA1c values, high neutrophil-lymphocyte ratio (NLR) values and DFUs

What does the study involve?

Participants are randomly allocated to one of two groups. Both groups will receive standard of care diabetes care and DFU wound treatment. Patients in the treatment group will additionally receive five subsequent once-a-week infusions of WF10.

What are the possible benefits and risks of participating?

Previous clinical studies already showed that WF10 treatment reduced HbA1c values and inflammation and improved DFU wound healing. In rare cases, WF10 led to minor adverse events, including local irritations at the injection site.

Where is the study run from?

Universiti Kebangsaan Malaysia Medical Centre (UKMMC) (Malaysia)

When is the study starting and how long is it expected to run for?

June 2020 to February 2022

Who is funding the study?
OXO Translational Science GmbH (Germany)

Who is the main contact?
Assoc. Prof. Dr. Mohd Yazid Bajuri, yb@ppukm.ukm.edu.my

Contact information

Type(s)

Principal Investigator

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Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

Version 6.0

Study information

Scientific Title

Effect of WF10 on hemoglobin A1c, neutrophil-lymphocyte ratio values and advanced glycation end product formation in type 2 diabetes mellitus patients with diabetic foot ulcers

Study objectives

The application of WF10 as an adjunct for the treatment of diabetics with diabetic foot ulcers (DFU) is based on the following key assumptions regarding the Mode of Action (MoA) of the

drug:

1. The drug selectively removes highly glycated red blood cells (RBCs). The insulin-independent formation of these cells can be addressed via HbA1c, which is a known predictive factor for Diabetes-derived vascular complications. Highly glycated erythrocytes – named “sick” or sRBCs – are characterised by elevated endothelial binding, reduced deformability and a higher tendency towards hemolysis. For the detection of sRBCs both complete blood count (CBC) values (e.g. MCV, RDW-CV) and microscopic analysis will be used.

2. Accordingly, these cells contribute to vascular pathologies and local/systemic pro-inflammatory reactions in diabetics. The latter can be clinically addressed by determining the neutrophil-lymphocyte ratio (NLR), which is a known predictive clinical parameter for the development of type 2 diabetes mellitus (DM2)-derived vascular complications like peripheral arterial disease (PAD) and impaired wound healing at DFU. However, clinical studies showed multiple immune-modulatory effects of WF10, including the reduction of elevated NLR values.

3. Furthermore, based on in vitro experiments it can be assumed that the chlorite component of WF10 directly inactivates/scavenges the main hemolytic products, namely free hemoglobin and free heme. These products also contribute to both, vascular pathologies and immunological disturbances. Moreover, hemolytic products may induce new hemolytic events (auto-hemolysis), a process which is most likely also stopped by WF10.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Approved 26/06/2020, Research Ethics Committee, The National University of Malaysia (Tingkat 1, Blok Klinik, Hospital Canselor Tuanku Muhriz, Pusat Perubatan UKM, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras Kuala Lumpur, Malaysia, +60 (0)3 9145 5046/5048; sepukm@ukm.edu.my), ref: UKM PPI/111/8/JEP-2020-221

Study design

Monocentric interventional randomized controlled two-arm trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied

Diabetic patients with elevated HbA1c values, elevated NLR values and DFU

Interventions

The drug WF10 will be applied via intravenous infusion by using a dose of 0.3 ml/kg body weight (BW). Thereby the appropriate drug amount will always be diluted in 300 ml physiological saline for an intravenous 2 h infusion. For each patient, one weekly infusion will be performed for five subsequent weeks (W00, W01, W02, W03, W04). The study will be conducted as a single-center two-arm parallel-group trial. The randomization is organized in Malaysia via sealed envelopes and a randomization list. Both arms will receive standard-of-care (SoC) in regard to diabetic control and DFU treatment while one arm will additionally receive WF10 treatment.

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

WF10/Immunokine(R)

Primary outcome measure

HbA1c measured using blood sample at Screen, baseline, week 4, week 6, week 8, week 12

Secondary outcome measures

1. Routine clinical laboratory safety tests (fasting morning) at Screen, baseline, week 4, week 6, week 8, week 12:

1.1. Hematology: RBC, hemoglobin (Hb), haematocrit (HCT), red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte (RTC), platelet (PLT), white blood cell (WBC) (absolute and differential), calculated NLR

1.2. Coagulation: prothrombin time (PT, international normalized ratio [INR]), activated partial thromboplastin time (aPTT)

1.3. Routine clinical chemistry: aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyl transpeptidase (gGT), alkaline phosphatase, lactate dehydrogenase (LDH), total and direct bilirubin, creatinine, urea, uric acid, glucose, total protein, albumin, triglycerides, total cholesterol, sodium, potassium, calcium, chloride, phosphorus, bicarbonate; calculated estimated glomerular filtration rate (eGFR)

1.4. Semi-quantitative urinalysis (Dip-Stick): microalbumin excretion

1.5. Quantitative (spot sample): albumin-creatinine, sodium-creatinine and cystatin C-creatinine ratio (UCCR)

2. Full blood picture with complete blood count (see above) and microscopic evaluation and interpretation of the blood cell morphology at baseline, week 4, week 6, week 8, and week 12. During the microscopic blood cell evaluation, photographic images of the blood smears shall be taken for electronic documentation.

3. Blood pressure and pulse rate measured by means of an automated oscillometric device at Screen, baseline, week 1, week 2, week 3, week 4, week 6, week 8, week 12

4. 12-lead ECG (rhythm, PQ, QRS, QT, QTc, clinical diagnosis/evaluation) at Screen, (Baseline), and week 12

5. AGE determination using blood and urine samples at Screen, baseline, week2, week 4, week 8

6. DFU assessment at baseline, week 4, week 8, and week 12 using:

6.1. Wall shear stress (WSS) and wound topography evaluation

6.2. Patient questionnaire on quality of life

6.3. Radiography for osteomyelitis evaluation

6.4. Assessment and documentation (photos) by an independent assessor

Overall study start date

26/06/2020

Completion date

28/02/2022

Eligibility

Key inclusion criteria

1. Male and female patients, at least 18 years of age, maximum age 80 years
2. Body mass index (BMI) $<35 \text{ kg/m}^2$
3. Diabetes mellitus type 2, diagnosed since at least 1 year and presently treated with standard care for at least 3 months prior to enrolment
4. Patients with active diabetic foot problems, according to the diabetic foot stratification table, starting at least 3 weeks prior to enrolment or infected wound degree 3 – 4
5. HbA1c $\geq 8.0 \%$ (63.9 mmol/mol)
6. NLR: 3 – 35
7. No or mild anemia (Hct $\geq 27 \%$, Hb $\geq 9.0 \text{ g/dl}$)
8. No blood transfusion within the last 2 months before screening
9. eGFR = 30 – 89 ml/min/1.73 m² BSA (Grades 2 – 3b)
10. Urinary microalbumin excretion $<300 \text{ mg/l}$
11. Urine Albumin-Creatinine Ratio (uACR) $\leq 300 \text{ mg/g}$ (Categories A1 – A2)
12. Having good vein access
13. Willing and able to adhere to the study regulations including attendance to the scheduled visits to the trial site
14. Willing and able to provide informed consent

Inclusion criteria for females:

1. Women of Childbearing Potential (WOCBP) presently on standard of care with hormonal treatment (including hormonal contraception) for at least 3 months prior to enrollment
2. WOCBP who are not on contraception shall be advised on Barrier Protection or Copper Intrauterine Device (IUD)

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

20

Total final enrolment

20

Key exclusion criteria

1. Previous participation in any clinical trial within the last 3 months before screening
2. Previous treatment with WF10 within the last 4 months
3. Karnofski performance status <70
4. Evidence or suspicion that the patient is reliable and/or might have difficulty complying with protocol-defined restrictions including the visit schedule
5. Suspicion or evidence of alcohol, medication or drug abuse
6. Comorbidity that might put the trial participant at risk or might confound the interpretation of the study outcome; this includes, but is not limited to (at the investigator's discretion):
 - 6.1. Patients with glucose-6-phospho-dehydrogenase deficiency, severe thalassemia, clinically unstable patients e.g. with clinically significant cardiac (e.g. ischemic heart disease, congestive failure, heart arrhythmia), vascular (including uncontrolled hypertension), pulmonary, musculoskeletal, endocrine (other than diabetes), hepatic, biliary, urogenital, neurological or psychiatric disease and/or malignancy
 - 6.2. Patients with acquired brain injury (ABI) <0.8
 - 6.3. Rapidly progressing renal disease due to causes other than diabetes mellitus
 - 6.4. Patients who receive chemotherapeutic drug during the enrolment
 - 6.5. Patients with history of organ transplantation, and using immunosuppressive drug
 - 6.6. Present or recent treatment with prohibited medication (see below)
 - 6.7. Surgery (unless minimal) or major trauma within the last 2 months before screening
7. Abnormalities in clinical laboratory safety testing at screening judged to be clinically significant by the investigator, including - but not limited - to:
 - 7.1. Liver enzymes (ALT, AST or g-GT) >3x upper limit of normality
 - 7.2. Serum K⁺ >6.0 or <3.0 mEq/l

Exclusion criteria for females:

1. Pregnant or lactating
2. NOT surgically sterile
3. NOT taking medically adequate contraception

Date of first enrolment

11/11/2020

Date of final enrolment

18/11/2021

Locations

Countries of recruitment

Malaysia

Study participating centre

Universiti Kebangsaan Malaysia Medical Centre (UKMMC)

Department of Orthopaedics and Traumatology

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Sponsor information

Organisation

OXO Translational Science GmbH

Sponsor details

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Industry

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Funder(s)

Funder type

Industry

Funder Name

OXO Translational Science GmbH

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal

Intention to publish date

31/08/2022

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available due to confidentiality reasons.

IPD sharing plan summary

Not expected to be made available

