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

Submission date	Recruitment status	[ ] Prospectively registered
11/08/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
12/08/2022	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
12/08/2022	Nutritional, Metabolic, Endocrine	[ ] 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

Protocol serial number
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 Klinikal, Hospital Canselor Tuanku Muhriz, Pussat 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

Primary study design
Interventional

Study design
Monocentric interventional randomized controlled two-arm trial

Study type(s)
Treatment

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(s)

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

Key secondary outcome(s)
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

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 kg/m²
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 ≥8.0 % (63.9 mmol/mol)
6. NLR: 3 – 35
7. No or mild anemia (Hct ≥27 %, Hb ≥9.0 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 mg/l
11. Urine Albumin-Creatinine Ratio (uACR) ≤300 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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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
Jalan Yaacob Latif, 56000 Bandar Tun Razak, Cheras
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Sponsor information

Organisation
OXO Translational Science GmbH

Funder(s)

Funder type
Industry

Funder Name
OXO Translational Science GmbH

Results and Publications

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