A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess Cardiovascular Outcomes Following Treatment with MK-3102 in Subjects with Type 2 Diabetes Mellitus

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Program-specific Objective:To assess the impact of MK-3102 25 mg q.w. on time to confirmed CV outcomes as measured by the time to first event in the CVcomposite endpoint of CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON40095

Source
ToetsingOnline

Brief title
OMNEON*-018

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
non-insulin-dependent diabetes, type 2 diabetes mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck

Intervention

Keyword: Cardiovascular, Phase 3, Type 2 Diabetes mellitus

Outcome measures

Primary outcome

To assess the safety and tolerability of MK-3102 25 mg q.w.

Secondary outcome

To assess the impact of MK-3102 25 mg q.w. on:

a. change from baseline in A1C over time;

b. in subjects not receiving insulin at baseline, time to initiation of

long-term insulin therapy (long-term insulin therapy is defined as a continuous

period of insulin use of more than 3 months).

Study description

Background summary

MK-3102 is a novel dipeptidyl peptidase-IV (DPP-4) inhibitor that is in Phase III clinical
development for the treatment of patients with T2DM. Unlike the presently marketed
DPP-4 inhibitors, which are administered once- or twice-daily, MK-3102 has a half-life
that supports once-weekly dosing. T2DM is associated with an elevated risk of cardiovascular (CV) disease, which is the leading cause of morbidity and mortality in this
patient population. In recent years, regulatory agencies including the United States Food
and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada have mandated that, prior to filing for marketing approval, new

antihyperglycemic agents (AHA) developed to treat T2DM undergo an enhanced CV-risk
assessment. Details of the required assessment vary between the EMA and FDA/Health
Canada, but the guidelines of each state that patients at higher risk of CV events should
be included in Phase II and Phase III studies in numbers sufficient to allow a metaanalysis
(pooled analysis) to evaluate the CV safety profile of the new medication. The FDA guidance also requires that Sponsors establish an independent CV endpoints committee to prospectively, and in a blinded manner, adjudicate CV events occurring
during the clinical development program. The present trial was designed to address these
requirements and the data will, therefore, contribute to the assessment of the safety
profile of MK-3102, including the requisite assessment of the CV safety profile.

Study objective

Program-specific Objective:
To assess the impact of MK-3102 25 mg q.w. on time to confirmed CV outcomes as measured by the time to first event in the CV
composite endpoint of CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization.

Study specific Objective:
When added to usual background therapy in subjects with T2DM and established CV disease with inadequate glycemic control:
To assess the effect of treatment with MK-3102 25 mg q.w. compared with placebo on A1C.

Insulin Sub-study-specific Objectives:
In subjects with T2DM and established CV disease with inadequate glycemic control on
insulin with or without metformin:

Objective: After 18 weeks, to assess the effect of MK-3102 25 mg q.w. as compared with placebo on A1C.
Objective: To assess the safety and tolerability of MK-3102 25 mg q.w.

Study design

This is a multicenter, double-blind, randomized, placebo-controlled, parallel group, Phase

III clinical trial. Approximately 4,000 subjects with T2DM and established CV disease
who have inadequate glycemic control (A1C *7.0 and *10.0%) and who, at the time of
screening, are being treated with a diabetis treatment regimen as specified in
the protocol will be randomized in a 1:1 ratio to MK-3102 25 mg q.w. or placebo.

There will be a 2 week run in period where all patients receive single blind
placebo before they are randomized.

The duration of the trial will be "event driven" and will continue at least
until the number
of confirmed CV events across the Phase II/III program is sufficient to meet
regulatory
requirements for the assessment of CV safety. It is estimated (based on a CV
event rate
of 2.25%) that subjects will participate in the trial for as long as 2.5 to 3
years. However,
the trial may be continued and expanded (by amendment) post-filing for further
CV
assessment. An external data monitoring committee (DMC) will be monitoring this
trial
(and the entire Phase III program) and will be charged with overseeing the
conduct of the
trial.

Intervention

MK-3102 or placebo once weekly.

Study burden and risks

MK-3102 is a structurally distinct and potent DPP-4 inhibitor, which is being
developed for
the treatment of T2DM. Unlike the presently marketed DPP-4 inhibitors, which are
administered once- or twice-daily, MK-3102 has a t1/2 that supports once-weekly
dosing.
Weekly dosing of an efficacious, well-tolerated, safe, oral agent that reduces
pill burden has
the potential to increase adherence to AHA therapy, which in turn may improve
long-term
outcomes. Such an agent would represent a welcome addition to the existing
armamentarium
of oral agents for the treatment of T2DM and may help shape future treatment
paradigms. In developed
countries CV disease accounts for 65-75% of deaths in people with T2DM.

Monitoring of AE's ECG's, vital signs and lab safety tests will be performed to support patient safety and evaluation of the safety profile.

The risks and burden to the patient are thought to be in perspective to the treatment of the patient and the need to study new compounds with added benefits.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Having T2DM and is *40 years of age.;2. Subject is on one of the following diabetes treatment regimens that is stable for at least 12 weeks (except for pioglitazone for at least 16 weeks) and is within the associated A1C range for that treatment regimen:
- An A1C *6.5 and *10.0% (*48 mmol/mol and *86 mmol/mol) on

diet and exercise alone (not on an AHA for *12 weeks)
OR
monotherapy with metformin (MF); pioglitazone (PIO); an alpha-glucosidase inhibitor (AGI); or an SGLT2 inhibitor (SGLT2i)
OR
dual combination therapy with MF, PIO, AGI or SGLT2i
OR
- An A1C *7.0% and *10.0% (*53 mmol/mol and *86 mmol/mol) on
monotherapy with a sulfonylurea or meglitinide
OR
dual combination therapy with a sulfonylurea or a meglitinide and MF, PIO, AGI, or SGLT2i
OR
- An A1C *7.0% and *10.0% (*53 mmol/mol and *86 mmol/mol) on one of the following insulin regimens (with or without metformin)
basal insulin (e.g., insulin glargine, insulin detemir, NPH insulin, degludec)
prandial insulin (e.g., regular, aspart, lispro, glulisine)
basal/prandial insulin regimen consisting of multiple dose insulin injections of basal and prandial insulin or the use of pre-mixed insulin (e.g., Novolog 70/30®, Novolin 70/30®, Humalog 75/25®, or Humulin 70/30®);3. Having following preexisting vascular disease:;(a) History of a major clinical manifestation of coronary artery disease (i.e., myocardial infarction, surgical or percutaneous [balloon and/or stent] coronary revascularization procedure, or coronary angiography showing at least one stenosis *50% in a major epicardial artery or branch vessel);;(b)Ischemic cerebrovascular disease, including:;- History of ischemic stroke ;- History of carotid arterial disease as documented by *50% stenosis documented by carotid ultrasound, magnetic resonance imaging (MRI), or angiography, with or without symptoms of neurologic deficit.;(c) Atherosclerotic peripheral arterial disease, as documented by objective - amputation due to vascular disease, current symptoms of intermittent claudication confirmed by an ankle-brachial pressure index of less than 0.9 or a toe-brachial pressure index less than 0.7 or history of surgical or percutaneous revascularization procedure.;4.Meets one of the following criteria:;a. Subject is a male ;b. Subject is a female not of reproductive potential defined as one who has either:;(1) reached natural menopause (defined as *12 months of spontaneous amenorrhea in women >45 years of age, or *6 months of spontaneous amenorrhea with serum follicular stimulating hormone [FSH] levels in the postmenopausal range as determined by the laboratory), or ;(2)had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to screening;c. Subject is a female of reproductive potential and:;1. agrees to remain abstinent from heterosexual activity (if this form of birth control is accepted by local regulatory agencies and ethics review committees as the sole method of birth control) or;2. agrees to use (or have their partner use) acceptable contraception to prevent pregnancy within the projected duration of the trial and for 21 days after the last dose of blinded study medication. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include:;*Use of one of the following double-barrier methods:diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom. ;*Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with one of the following:diaphragm with spermicide; cervical cap; contraceptive sponge;

condom; vasectomy; or intrauterine device (IUD).;*Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge, vasectomy; or hormonal contraception (see above).;* Vasectomy with one of the following:diphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above). ;5. Understanding the trial procedures, alternative treatments available, providing the providing written informed consent, consent for Future Biomedical Research can be provided (not obligatory).

Exclusion criteria

1. History of type 1 diabetes mellitus or a history of ketoacidosis or possibly having type 1 diabetes ;2. Beeing treated with rosiglitazone, a DPP-4 inhibitor or a GLP-1 receptor agonist within the prior 12 weeks of Visit 1/Screening or previously treated with MK-3102.;3. Having a history of hypersensitivity to a DPP-4 inhibitor;4. Participation in trial with investigational compound prior 12 weeks of signing the informed consent or is not willing to refrain from participating in another trial.;5. Subject is on a weight loss program and is not in the maintenance phase; has been on a weight loss medication in the past 6 months; or has undergone bariatric surgery within 12 months prior to signing the informed consent.;6. Surgical procedure within 4 weeks prior to signing informed consent or has planned major surgery during the trial.;7. Treatment for *14 consecutive days or repeated courses of pharmacologic doses of corticosteroids;8. Treatement for hyperthyroidism or thyroid replacement therapy and has not been on a stable dose for at least 6 weeks.;9. Medical history of active liver disease;10. Human immunodeficiency virus (HIV) as assessed by medical history.;11. Worsening signs or symptoms of coronary heart disease or congestive heart failure within the past 3 months.;12. Poorly-controlled hypertension ;13. History of malignancy *5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.;14. Clinically important hematological disorder;15. Exclusionary laboratory values;16. Positive urine pregnancy test.;17.Subject is pregnant or breast-feeding, or is expecting to conceive during the trial, including 21 days following the last dose of blinded study medication. OR is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 21 days following the last dose of blinded study medication.;18. Subject is,at the time of signing informed consent,a user of recreational or illicit drugs or has had a recent history of drug abuse.;19. Subject routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per;week, or engages in binge drinking.;20. History or current evidence of condition, therapy, lab abnormality or other circumstance that;*makes participation not in the subject*s best interest;*might interfere with subject*s participation for the full duration of the trial, or;*might confound the result of the trial.;21.Subject has donated blood products or has had phlebotomy of >300 mL within 8 weeks of signing informed consent, or intends to donate blood products within the projected duration of the trial OR received, or anticipated to receive blood products within 12 weeks of signing informed consent or within the projected duration of the trial.;22. Subject is unlikely to adhere to the trial procedures, keep appointments.;23.Symptomatic hyperglycemia that, in the investigator's opinion, requires immediate initiation, adjustment, or addition of AHA therapy or has a FPG consistently (i.e., measurement repeated and confirmed within 7 days) >260 mg/dL (14.4

mmol/L).;24.Clinically significant ECG abnormality which in the opinion of the investigator exposes the subject to risk by enrolling in the trial.;25.Poorly controlled hypertension defined as systolic blood pressure of *160 mm Hg or diastolic blood pressure of *90 mm Hg.;26.Subject is on lipid-lowering medication or thyroid replacement therapy, and has not been on a stable therapy for the 4 weeks (lipid-lowering medication), or 6 weeks (thyroid replacement therapy) prior to Visit 3/Day 1. In this case the current visit can be changed to an Unscheduled Visit, and the subject should be rescheduled for a Visit 3/Day 1.;27.Subject has a positive urine pregnancy test.;28.Subject has a site fasting-fingerstick glucose (FFSG) <126 mg/dL (7.0 mmol/L) or >260 mg/dL (14.4 mmol/L).;29.Subject has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described trial exclusion criteria or which, in the opinion of the investigator, exposes the subject to risk by enrolling in the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2013
Enrollment:	139
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MK-3102
Generic name:	nvt

Ethics review

Approved WMO Date:	04-10-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-05-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002414-39-NL
CCMO	NL41552.091.12