A Phase 3, Randomized, Double-blind Study of Siltuximab (Anti-IL-6 Monoclonal Antibody) or Placebo in Combination With VELCADE and Dexamethasone for the Treatment of Subjects With Relapsed or Refractory Multiple Myeloma

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON36750

Source
ToetsingOnline

Brief title
CNTO328MMY3001

Condition

- Plasma cell neoplasms
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's Disease, Multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen Biologics B.V. (voordien gekend als Centocor B.V) vertegenwoordigd door Global Clinical Operations
Source(s) of monetary or material Support: Janssen Biologics B.V.

Intervention

Keyword: dexamethasone, multipele myeloma, Siltuximab, velcade

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is PFS according to the EBMT

criteria.

Secondary outcome

Secondary efficacy endpoints include:

-Overall survival

-Overall response rate according to International Myeloma Working Group (IMWG)

and EBMT criteria

-Proportion of subjects with increase in hemoglobin of >= 2 g/dL from baseline

without erythropoietin

stimulating agent (ESA) use or blood transfusions

-Duration of response

Study description

Background summary

Preclinical and preliminary clinical experience support combining siltuximab

with
VELCADE and dexamethasone in this patient population. In addition, siltuximab has
been shown to be safe when given in combination with the 3-drug regimen, VELCADEmelphalan-
prednisone. The VELCADE + low-dose dexamethasone regimen selected as comparator is a widely used standard of treatment for relapsed or refractory multiple
myeloma that has shown incremental benefit over VELCADE alone .
VELCADE + low-dose dexamethasone has been well tolerated in dosing regimens that exceed 1 year of continuous treatment including
studies where VELCADE re-treatment has been offered to previously responding patients.
This study has been designed to fully evaluate the benefit:risk of siltuximab when added to the standard regimen of VELCADE + low-dose dexamethasone

Study objective

The primary objective of this study is to determine if there is an improvement in progression-free survival
(PFS) when siltuximab is added to VELCADE* (bortezomib) and dexamethasone in subjects with relapsed
or refractory multiple myeloma.
The secondary objectives of this study are to assess safety, additional measures of clinical benefit,
patient-reported outcomes (PROs), pharmacokinetics of dexamethasone and siltuximab, antibodies to
siltuximab (immunogenicity), exploratory biomarkers, and health economic outcomes.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study. Approximately
500 subjects with relapsed or refractory multiple myeloma will be randomized 1:1 to receive siltuximab,
VELCADE, and dexamethasone or placebo, VELCADE, and dexamethasone. The primary endpoint is
PFS according to the European Group for Blood and Marrow Transplantation (EBMT) criteria (Blade et al,
1998). The final analysis of the primary endpoint PFS will occur when 312 events (disease progression or
death) have been recorded. The final analysis of overall survival will occur after 280 deaths have been
recorded. This is expected to happen approximately 5 years after the first

subject starts study treatment.
The pharmacokinetics of dexamethasone when given with VELCADE alone, and in combination with
VELCADE and siltuximab will be determined from approximately 60 subjects (approximately 30 per
treatment arm) at selected clinical sites. Circulating multiple myeloma cells (CMMC) will be evaluated
from a minimum of 200 subjects at selected clinical sites.
An Independent Data Monitoring Committee (IDMC) will be established to ensure the continuing oversight
of the safety of subjects enrolled in this study.

Intervention

Approximately 500 subjects will be randomized 1:1 using an IVRS to 1 of the following blinded treatment
arms:
Arm A: Siltuximab, VELCADE, and dexamethasone - repeat every 21 days
- Siltuximab: 11 mg/kg, 1-hour IV infusion, Day 1
- VELCADE: 1.3 mg/m2 IV push, Days 1, 4, 8, 11 for Cycles 1 to 8; then Days 1 and 8 for
Cycle 9 and higher
- Dexamethasone: 20 mg orally, the day of and the day after VELCADE administration
Arm B: Placebo, VELCADE, and dexamethasone - repeat every 21 days
- Placebo: 1-hour IV infusion, Day 1
- VELCADE: 1.3 mg/m2 IV push, Days 1, 4, 8, 11 for Cycles 1 to 8; then Days 1 and 8 for
Cycle 9 and higher
- Dexamethasone: 20 mg orally, the day of and the day after VELCADE administration
No crossover between treatment arms will be allowed.

Study burden and risks

Screening Period: Screening should occur within 21 days before first study agent administration.
Treatment Period: Treatment will continue until disease progression, death, unacceptable toxicity despite
dose modification or delays, or withdrawal of consent for study treatment, whichever occurs first. Subjects
achieving confirmed CR should receive at least 2 additional cycles of the assigned treatment regimen.
Follow-up Period: All subjects will have follow-up visits 4 weeks (End of Treatment Visit), 8 weeks, and
12 weeks after the last study agent administration, and thereafter will be

followed up for survival every
3 months until the end of study. For subjects who discontinue study agents
before disease progression,
disease assessments should continue to be performed as scheduled until
confirmed disease progression,
death, the start of a new treatment for multiple myeloma, withdrawal of consent
for study participation, or
the end of study, whichever occurs first. Subjects with disease progression
should be followed up for
subsequent anti-multiple myeloma treatment and survival.
End of study definition: The study will end at the time of the final analysis,
which will be after
280 deaths have been recorded. This is expected to occur approximately 5 years
after the first subject starts
study treatment. Subjects who are benefiting from treatment (complete response
[CR] or partial response
[PR]) at the end of study may be eligible to receive siltuximab in a separate
protocol.

For the risks: see E9 of this document

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

-Males or females aged 18 years or above
-Confirmed diagnosis of multiple myeloma requiring treatment
-Measurable secretory disease
-Must have received 1 to 3 lines of prior treatment for multiple myeloma -Must have achieved a response (MR or better) to at least 1 prior line of treatment
-Must have progressed on or be refractory to the most recent line of treatment.
-Subjects must not be refractory to any previous line of treatment that included a proteasome inhibitor
See als protocol page 30

Exclusion criteria

-Diagnosis of primary amyloidosis, plasma cell leukemia, or other conditions in which a paraprotein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
-Grade 1 peripheral neuropathy with pain or Grade 2 or higher peripheral neuropathy
-Allogeneic bone marrow transplantation within 28 days before the first dose of study agent. Subjects for whom bone marrow transplant is planned within 12 months after study start are also ineligible.
-Chemotherapy or radiation therapy within 21 days before the first dose of study agent
-Clinically significant infection, including known HIV or hepatitis C infection, or known hepatitis B surface antigen positivity
-Significant cardiac disease characterized by significant ischemic coronary disease, significant arrhythmias, or congestive heart failure (NYHA Class III or IV) or myocardial infarction within 6 months before the first dose of study agent
-Known severe infusion related reactions to monoclonal antibodies or to murine, chimeric, or human proteins
-Prior exposure to agents targeting IL-6 or the IL-6 receptor
See also protocol pg 31

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:	Will not start
Start date (anticipated):	31-03-2011
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	dexamethasone
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Siltuximab (CNTO328)
Generic name:	Siltuximab (CNTO328)
Product type:	Medicine
Brand name:	Velcade
Generic name:	bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-03-2011
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	09-05-2011
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2009-017237-22-NL
CCMO	NL35314.075.11