A phase II, double blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy

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Primary objective: • To assess the efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 24 weeks in ambulant subjects with DMD.Secondary objectives:• To assess the safety and tolerability of 2 different dosing…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON34487

Source
ToetsingOnline

Brief title
GSK2402968 in subjects with Duchenne muscular dystrophy

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Duchenne muscular dystrophy

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Keyword: Duchenne muscular dystrophy, Efficacy, Pharmacokinetics, Safety

Outcome measures

Primary outcome

Primary efficacy endpoint:

• Muscle function using 6 minute walking distance (6MWD) test

Secondary outcome

Secondary efficacy endpoints:

• Timed function tests (times and grading):

- rise from floor

- 10m walk/run

- 4-stair climb

• Muscle strength (total score): knee flexors, knee extensors, elbow flexors,

elbow extensors, shoulder abductors and hip flexors (as determined by handheld

dynamometry)

• North Star Ambulatory Assessment

• Creatine kinase serum concentrations

• Pulmonary function (FEV1, FVC, MIP, MEP, PCF, PF)

• Dystrophin expression (muscle biopsies)

• Pediatric Quality of Life Neuromuscular module (exploratory endpoint)

Safety endpoints:

• Adverse events

• Physical examination including local tolerability

• Vital signs

• ECG parameters

• Safety haematology and biochemistry parameters including non-standard parameters such as coagulation parameters (in particular aPTT), cystatin C, Compliment factor C3, haptoglobulin, fibrinogen, CRP

• Urinalysis (including quantitative protein, creatinine and ratio in urine and α microglobulin)

• Echocardiogram

Pharmacokinetics:

Blood samples for PK analysis will be taken at intervals and sparse sampling techniques will be used. This data will be combined with data from other studies with GSK2402968 and reported separately as part of a population PK modelling analysis.

DEXA Scan

• Lean body mass (exploratory endpoint)

Pharmacogenetics:

Saliva samples for pharmacogenetic (PGx) analysis will be collected at the randomisation visit. The extracted DNA will be evaluated for an association

between genetic variation and response (safety, tolerability, PK, and efficacy)

following treatment with GSK2402968, if warranted.

Gait characterisation collected by accelerometry during 6MWD test and free walk

test (exploratory endpoint)

Study description

Background summary

At the moment, there is no treatment available to prevent the progression of DMD. Glucocorticosteroids are used as the current standard of care but they do not alter the fundamental course of this seriously disabling and ultimately fatal disease. New treatments are needed that can help to relieve the symptoms of this disease and prolong the lifespan and quality of life of affected individuals.

GSK2402968 has been explored at doses up to 6 mg/kg subcutaneous weekly initially for 5 weeks in ambulant subjects with DMD. An open-label extension protocol is ongoing, and to date subjects have received GSK2402968 6 mg/kg/week for at least 3 months. GSK2402968 appears to be well tolerated and has the potential to be effective however, more information is needed to determine dosing regimens for to ensure an effective dose with minimal side effects for the subject.

Study objective

Primary objective:
• To assess the efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 24 weeks in ambulant subjects with DMD.

Secondary objectives:
• To assess the safety and tolerability of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
• To assess the PK of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
• To assess long term efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.

Study design

This is a phase II, double-blind, exploratory, parallel-group, placebo-controlled clinical study in ambulant subjects with DMD resulting from a mutation that can be corrected by exon skipping induced by GSK2402968.

The study aims to randomise 54 subjects, which assuming a drop-out rate of approximately 10%, should provide 48 evaluable subjects. There will be 2 parallel cohorts. Each cohort will include 16 subjects on GSK2402968 and 8 subjects on matched placebo (2:1 ratio).

The active doses will be:
• Continuous regimen; 6mg/kg GSK2402968 once weekly
• Intermittent regimen; 6mg/kg GSK2402968 twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle

All subjects will receive a loading dosing regimen of twice weekly dosing with 6 mg/kg GSK2402968 or placebo for the first 3 weeks of treatment. The intermittent regimen cycles will start after completion of the loading dosing regimen (i.e. from Week 4).
The study will be fully blinded with respect to active and placebo in each cohort, however the different regimens will not be fully blinded. Subjects allocated to the continuous dosing regimen will receive a total of 51 doses of GSK2402968 or placebo, whereas subjects allocated to the intermittent regimen will receive a total of 50 doses of GSK2402968 or placebo.

Prior to randomisation, subjects will have two screening visits. At the first screening visit (2-4 weeks prior to the first dose) full safety and efficacy measurements will be undertaken to evaluate eligibility. At the second screening visit (up to 2 weeks prior to the first dose), two of the efficacy assessments (6-Minutes Walking Distance [6MWD] and *rise-from-floor*) will be conducted as well as laboratory safety assessments. Results from both screening visits must be available prior to randomisation.

Subjects will be treated for 48 weeks (including the loading dose period) following a 2 to 4 week screening period. At the end of the treatment period, subjects who have completed the study may be entered into an extension study. Subjects who withdraw from the study for any reason will not be eligible for an extension study. Any subjects who do not enter the extension study, for whatever reason, will be monitored as clinically indicated but for a minimum of 20 weeks after the last dose of GSK2402968/placebo. A formal follow-up visit will be conducted 20 weeks after the last dose of GSK2402968/placebo.

If a subject withdraws from the study (but does not withdraw consent), he will have an Early Termination Visit as soon as possible after withdrawal, and will

then be followed up for safety and progress as clinically indicated, but for no less than 20 weeks after the last dose of study treatment. A formal follow-up visit will be conducted 20 weeks after the last dose of GSK2402968/placebo. If subjects withdraw, they will not be replaced.

Safety and efficacy will be measured at intervals throughout the study. An Independent Data Monitoring Committee (IDMC) will oversee the study and will regularly evaluate safety and tolerability, according to the IDMC charter.

The primary efficacy analysis for this study will be conducted when all subjects have completed 24 weeks of dosing. All subjects will remain on study until the final efficacy evaluations after 48 weeks of dosing.

Selected investigational sites will be involved in the collection of exploratory accelerometry data for gait characterisation. It is expected that 20 subjects from these sites will enter the accelerometry ancillary part of the protocol.

Intervention

Study Drug
*All patients will received 2 doses of the study drug per week for the first 3 weeks administered by subcutaneous injection.
*Patients will then follow one of two regimens:
- The continuous regimen group will receive the study drug administered by subcutaneous injection weekly
- intermittent regimen group will receive the study drug administered by subcutaneous injection at the following timepoints: : twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle

Muscle Biopsy
Both groups will undergo 3 muscle biopsies during their participation in the study

DEXA Scan
Both groups will undergo 3 DEXA scans during their participation in the study

Venipuncture
26 blood samples will be taken from each patient during their participation in the study

Study burden and risks

Because GSK2402968 is an experimental drug and there might be risks that are unknown or unforeseen at the moment. The following side effects have been

reported in patients who received GSK2402968 and these side effects can cause a risk for patients participating in the study:

•Skin reactions at the injection site* the study medication may cause all, some or none of the following at the site of the injection:
- redness,
- swelling,
- hardening of skin
- itching,
- irritation,
- pain.

•At the site of injection, the subject may experience minor bleeding, causing a bruise in the skin.

Blood Tests:
•A number of blood samples will be taken during the course of the study. There is a chance of a minor bleeding when taking blood as well as bruising at the site of needle insertion.

Muscle Biopsy:
•After the muscle biopsy the subject may feel pain at the place of the biopsy. Patients usually find the pain easy to tolerate and they rarely need to take a painkiller. The muscle biopsy may leave a small scar and it is possible that the strength of that muscle might be slightly reduced in the short term.

DEXA Scan:
•There is a very low radiation risk from the DEXA body scan. The level of radiation that the subject will be exposed to each scan is the same as radiation from watching television.

All measures will be taken by the study team to ensure the subject is as comfortable as possible during the above mentioned procedures. The subjects health and well being will be monitored closely throughout the study by the study team and adverse events will be treated and follwed up as clinically indicated.

Contacts

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Scientific
GlaxoSmithKline

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Ambulant subjects with Duchenne muscular dystrophy resulting from a mutation in the DMD gene, confirmed by a state-of-the-art DNA diagnostic technique covering all DMD gene exons, including but not limited to MLPA (Multiplex Ligation-dependent Probe Amplification), CGH (Comparative Genomic Hybridisation), SCAIP (Single Condition Amplification/Internal Primer) or H-RMCA (High-Resolution Melting Curve Analysis), and correctable by GSK2402968-induced DMD exon 51 skipping
2. Aged at least 5 years
3. Male
4. Life expectancy of at least 1 year
5. Able to rise from floor in <=7 seconds (without aids/orthoses)
6. Able to complete the 6MWD test with a distance of at least 75m, In addition, results of 6MWD must be within 20% of each other at each pre-drug visit,
7. Results of 6MWD and rise-from-floor tests must be reproducible (within 20% for each test) between Screening Visits 1 and 2
8. Receiving glucocorticoids for a minimum of 6 months immediately prior to screening, with no significant change in total daily dosage or dosing regimen for a minimum of 3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen will not change significantly for the duration of the study
9. QTc <450msec (based on single or average QTc value of triplicate ECGs obtained

over a brief recording period). Note: QTc may be either QTcB or QTcF, and machine read or manual overread
10. Subjects must be willing to use adequate contraception (condoms or abstinence) for the duration of the study and for at least 5 months after the last dose of study drug
11. Willing and able to comply with all protocol requirements and procedures
12. Able to give informed assent and/or consent in writing signed by the subject and/or parent(s)/legal guardian (according to local regulations)
13. In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Exclusion criteria

1. Any additional missing exon for DMD that cannot be treated with GSK2402968
2. Current or history of liver or renal disease or impairment
3. Acute illness within 4 weeks of the first anticipated administration of study medication which may interfere with study assessments
4. Use of anticoagulants, antithrombotics or antiplatelet agents, previous treatment with investigational drugs, within 6 months of the first administration of study medication, and idebenone or other forms of Coenzyme Q10 within 1 month of the first administration of study medication
5. Current or anticipated participation in any investigational clinical studies
6. Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test at screening
7. Symptomatic cardiomyopathy. If subject has a left ventricular ejection fraction <45% at Screening, the investigator should discuss inclusion of subject in the study with the medical monitor
8. Children in Care. The definition of a Child in Care is a child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The
definition of a child in care does not include a child who is adopted or has an appointed legal guardian.

Study design

Design

Study phase:	2
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):	07-02-2011
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not available
Generic name:	Not available

Ethics review

Approved WMO

Date:	01-06-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	13-09-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	15-11-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	01-12-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-01-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-10-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2010-018412-32-NL
CCMO	NL32173.000.10
Other	Not yet available