Clinical trial of exon skipping

DMD114044

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DMD114044

a Phase III, Randomised, Double-blind, Placebo-controlled, Clinical Study to Assess the Efficacy and Safety of GSK2402968 in Subjects with Duchenne Muscular Dystrophy.

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Current status in the Czech Republic

National Authority for Drug Control (SÚKL)
approval - FEB 24, 2011

Multicentric ethic commitee, University Hospital Brno
approval - FEB 12, 2011

Local ethic commitee, University Hospital Praha-Motol
approval - JAN 12, 2011

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Investigational centres

- **Fakultní nemocnice Brno,**
  Dětská nemocnice, Klinika dětské neurologie, Černopolní 9, 625 00 Brno-Černá Pole
  Principal investigator Petr Vondráček
  Tel: +420 723 216 022, neurovon@volny.cz

- **Fakultní nemocnice v Motole,**
  Klinika dětské neurologie, V Úvalu 84, 150 06 Praha 5
  Principal investigator Jana Haberlová
  Tel: +420 224 433 301, jana.haberlova@lfmotol.cuni.cz

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Investigational drug

GSK2402968 (6 mg/kg) - „antisense oligonucleotide" (AON)

Mechanism of action:
Specific binding on the exon 51 of the DMD gene

restoration of the dystrophin synthesis

conversion DMD > BMD

randomisation GSK2402968 / PLACEBO 3 / 1

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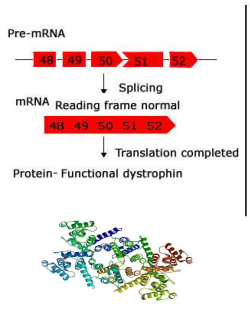
Normal dystrophin synthesis in a healthy individual



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- Duchenne muscular dystrophy caused by deletion of exon 50 in the *DMD* gene. This deletion puts two incompatible boundaries together in the spliced mRNA, resulting in a shift of the open reading frame that generates a downstream nonsense sequence, leading to premature termination of translation. Truncated and non-functional dystrophin in muscle fibres causes a severe DMD phenotype.

- Skipping of exon 51 induced by antisense oligonucleotide (AON). The splicing of exon 49 to 52 leaves the open reading frame undisturbed so that the mRNA can be translated into a slightly shortened but partially functional dystrophin, resulting in a significantly milder BMD phenotype.

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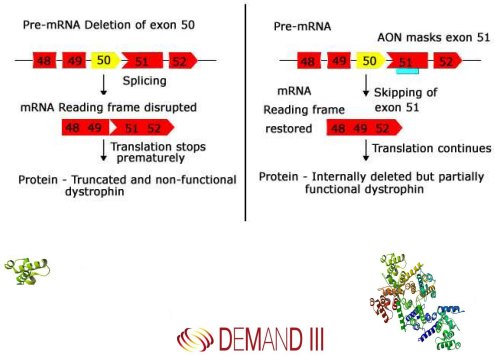

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Main inclusion criteria

- Informed consent of both parents and the patient
- MLPA verified DMD deletions of exons:
- 13-50, 29-50, 43-50, 45-50, 47-50, 48-50, 49-50, 50, 52
  13 % of the DMD population
- Age > 5 years
- Glucocorticoid treatment > 6 months,
  no change of dosage min. 3 months.
- 6 min walk test > 75 m during first 3 visits

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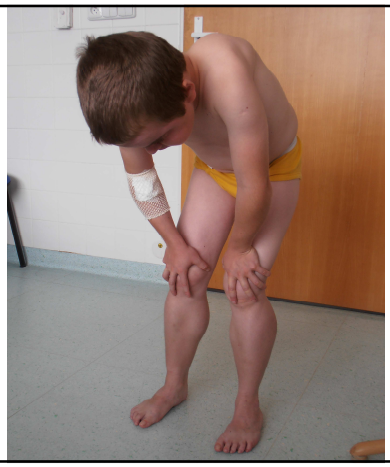

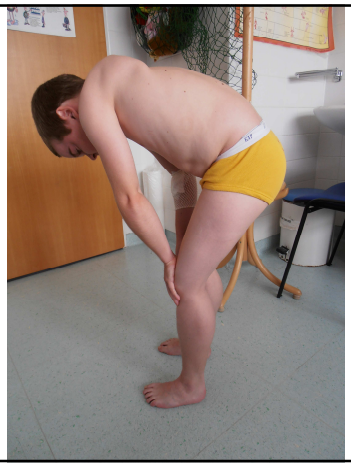

Main exclusion criteria

- Different mutation
- Participation in other clinical trials
- Anticoagulation, antithrombotic treatment. Other inestigational drugs during 6 months prior to this clinical trial. Idebenone or coenzyme Q10 during 1 month prior to this clinical trial.
- Symptomatic cardiomyopathy
- Liver or renal impairment

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Time schedule

Period prior to drug/placebo administration – 4 weeks (2 investigational visits)

Treatment period – 48 weeks

Investigational drug/placebo administration - S.C. injections 1/week into belly and other parts of a body

investigational visits – every week at the same day

Follow-up visit – 20 weeks after the last investigational visit

DMD114349 - a long term open label extension study

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Outcome measures

- 6 minute walk test (6MWT)
- Functional muscle tests – rise from the floor, 4 steps up and down, 10 mts walk, run
- Myometry – knee flexors and extensors, elbow flexors and extensors, shoulder abductors and hip flexors
- NSAA (North Star Ambulatory Assessment) – general mobility assessment
- Lung functions (spirometry)
- EKG and Echocardiography
- Whole body DEXA scan (bone densitometry)

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Monitored parametres and actions

- Biochemistry, blood count, urine analysis
- Farmacogenetics – saliva sample
- Farmacokinetics – 3x during treatment period
- Muscle biopsy – 2x
- Videorecordings - muscle function tests, general mobility assessment

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Recruitment

- Screened – CZ 6, worldwide 130
- Randomized – CZ 2, worldwide 86

Main problems:

- Loss of ambulation
- MLPA different deletion
- Inability to perform tests of muscle strength and function

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DMD114044 – information sources

www.léky.sukl.cz

www.clinicaltrials.gov

www.clinicaltrialsregister.eu

www.gsk-clinicalstudyregister.com

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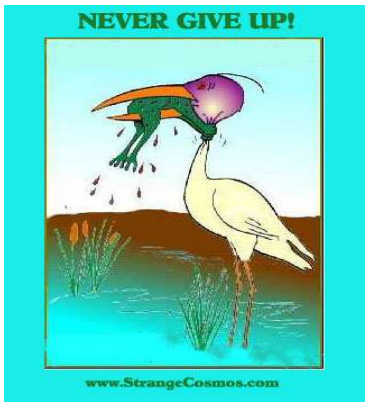

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