CareCN: A phase I/II, open-label, study to evaluate the safety and efficacy of an intravenous injection of GNT0003 (Adeno-associated Viral Vector expressing the UGT1A1 transgene) in patients with severe Crigler-Najjar syndrome requiring phototherapy

Published: 09-10-2017
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This study has been transitioned to CTIS with ID 2023-507007-60-00 check the CTIS register for the current data. Primary objectives:Dose escalation part:- To assess the safety and tolerability of an intravenous single-dose administration of GNT0003...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON52580

Source
ToetsingOnline

Brief title
Care CN

Condition

- Metabolic and nutritional disorders congenital

Synonym
Crigler-Najjar Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Généthon
Source(s) of monetary or material Support: Généthon & European Committee

Intervention

Keyword: Crigler-Najjar Syndrome, hyperbilirubinemia, metabolic disease

Outcome measures

Primary outcome

Primary Endpoint:

Dose escalation part:

- Incidence of treatment-emergent adverse events (TEAEs) or treatment-emergent serious adverse events (TESAEs) up to Week 17

- Change in laboratory parameters, vital signs and in physical examination from baseline to Week 17

Confirmatory part:

- The proportion of patients having received the selected dose of GNT0003 with serum total bilirubin = 300 µmol/L at Week 48 after IMP infusion and without phototherapy from Week 16

Secondary outcome

Secondary Endpoint:

Dose escalation part:

- Time to GNT0003 vector clearance from blood, urine, saliva and feces

- Number of patients with serum total bilirubin <= 300 µmol/L within 7 days

after interruption of daily phototherapy

Confirmatory part:

- Incidence of treatment-emergent adverse events (TEAEs) or treatment-emergent

serious adverse events (TESAEs) up to Week 48

- Change in laboratory parameters, vital signs and in the physical examination

from baseline to Week 48

- Change in serum total bilirubin from baseline to Week 48

- Change in bilirubin/albumin ratio from baseline to Week 48

- Change in Health-related quality of life, as measured by SF-36 (adult) and

PedsQL (pediatric), at Weeks 24 and 48

- Time to GNT0003 vector clearance from blood, urine, saliva and feces

Study description

Background summary

Adeno*associated virus (AAV) vector*mediated gene therapy has shown promising results in preclinical animal models and, more recently, in humans ((Kaplitt et al. 2007); (Maguire et al. 2008); (Nathwani et al. 2011); (Nathwani et al. 2014). Long*term correction of inherited diseases has been documented following AAV vector mediated gene transfer (Mingozzi and High 2011) and, notably, long* term transgene expression following liver gene transfer has been documented in liver in dogs (Niemeyer et al. 2009), non*human primates (Nathwani et al. 2011), and humans (Nathwani et al. 2014). The investigational medicinal product (rAAV8*hUGT1A1 - Product code GNT0003) is a genetically modified recombinant viral vector composed by the viral capsid of the serotype 8 of the AAV and a modified single stranded genome containing the cDNA sequence encoding for the human UGT1A1 transgene. The rAAV8*UGT1A1 has high tropism for liver and

expresses the UGT1A1 transgene predominantly in hepatocytes following cell transduction. This should allow for restoration of glucuronidation of bilirubin and subsequent excretion into the bile, which will prevent its accumulation into the blood. Overall, the good safety profile of recombinant AAV vectors demonstrated in preclinical and clinical studies, the prospect for sustained therapeutic effect thanks to the long*lived presence
of the viral vector genome, and the non*invasiveness of the administration route proposed (peripheral vein infusion) make the intravenous administration of the rAAV8*hUGT1A1 vector an attractive strategy for the treatment of CN syndrome.

Study objective

This study has been transitioned to CTIS with ID 2023-507007-60-00 check the CTIS register for the current data.

Primary objectives:

Dose escalation part:
- To assess the safety and tolerability of an intravenous single-dose administration of GNT0003 in patients with severe Crigler-Najjar syndrome requiring phototherapy

Confirmatory part:
- To assess the efficacy of the intravenous single-dose administration of GNT0003 selected dose in patients with severe Crigler-Najjar syndrome requiring phototherapy

Secondary objectives:
Dose escalation part:
- To assess the pharmacokinetics of GNT0003
- To assess the efficacy of the intravenous single-dose administration of GNT0003 in patients with severe Crigler-Najjar syndrome requiring phototherapy

Confirmatory part:
- To assess safety of the intravenous single dose administration of GNT0003 selected dose
- To evaluate the impact of GNT0003 selected dose in patients' Quality of Life
- To assess pharmacokinetics of GNT0003 selected dose
- To assess pharmacodynamic effect of GNT0003 selected dose

Study design

A phase I/II, open-label, single-group, multi-center, dose escalation and confirmatory study, followed by a long-term safety follow-up period. The study will enroll approximately 17 CN patients and will be conducted in 3 parts:
- Part 1: the dose escalation study, to assess 2 doses of GNT0003. The dose escalation part will include 2 cohorts of a maximum of 3 adult patients
- Part 2: the confirmatory study, to assess the efficacy and safety of the selected dose from part 1. At the confirmatory part, 11 additional patients >= 10 years old will be enrolled
- Part 3: the long-term follow-up study, to monitor delayed adverse events of all patients enrolled in part 1 and part 2 and to assess the sustainability of GNT0003 efficacy

Intervention

One intravenous infusion via peripheral vein of 200 mL of GNT0003 diluted in saline and human serum albumin

Study burden and risks

This is the first time that GNT0003 will be taken by humans, however it is thoughts that the risks associated are very low. In fact, GNT0003 has been studied in rats, and no adverse effects have been reported.
In humans, in previous studies conducted with the same type of vector (rAAV8) but in diseases other than Crigler-Najjar syndrome, an elevation of certain liver enzymes, called transaminases, has been observed. This elevation has been controlled by administering corticosteroids for a short period of time, which was followed by a quick return of these enzymes to their normal values. For this reason, in this study you will be asked to take oral corticosteroids (prednisolone) starting from the day before the injection of the experimental treatment and for the following four weeks to prevent this elevation
Blood samples for dosing liver enzymes will be taken regularly to check your levels and maintain a safe level Therefore, if an elevation is observed, your doctor can take the appropriate measures, such as resuming treatment with corticosteroids
In addition to the effects described above, GNT0003 may have other risks that at this point which are still unknown. Please also note that by receiving gene therapy a person may no longer donate blood or an organ.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Main Inclusion criteria
[1] Patients with severe Crigler-Najjar syndrome requiring daily phototherapy (>= 6h/day)
[2] Molecular confirmation of mutations in the UGT1A1 gene by DNA sequencing

Exclusion criteria

Main Exclusion criteria
[1] Fibrosis score >= 3 (METAVIR) or 10 PKa
[2] Patients who underwent liver transplantation

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-05-2018
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	09-10-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2018
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-09-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	12-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2022
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
EU-CTR	CTIS2023-507007-60-00
EudraCT	EUCTR2017-000506-37-NL
ClinicalTrials.gov	NCT03466463
CCMO	NL62978.000.17