2 SYNOPSIS

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Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

Title of Study:

A prospective non-therapeutic study in patients diagnosed with Niemann-Pick disease type C in order to characterise the individual patient disease profile and historic signo-symptomatology progression pattern

Investigators and Study Centres:

The study was conducted at 12 sites in 7 countries: 1 in Denmark, 2 in Germany, 4 in Italy, 1 in Poland, 1 in Spain, 1 in Switzerland and 2 in the United Kingdom.

Publication (Reference):

Not applicable.

Study Periods:	**Phase of Development:**
First patient screened: 09 October 2015 First patient enrolled: 09 October 2015 Last patient completed: 10 May 2017	Non-therapeutic, interventional

Objectives:

Primary:

- To characterize the individual patient disease progression profile (disease burden and progression) through the clinical, imaging, biological status, and Quality of Life prospectively recorded, together with the historic disease information collected from patient medical records.

Secondary:

- To evaluate the safety data of the disease-related therapy and to record every adverse event (AE) linked to the disease.

Methodology:

Prospective, non-therapeutic, interventional

Number of Patients (Planned and Analysed):

Planned:

At least 40 evaluable patients. Enrolment may have included up to forty-six (46) Niemann-Pick disease type C (NPC) patients.

Name of Sponsor/Company: Orphazyme A/S	**Individual Study Table Referring to Part of the Dossier** **Volume** **Page**	**(For National Authority Use only)**
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

Analysed:

A total of 36 patients were enrolled into the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

- Written informed consent (and assent if appropriate to local laws and regulations) prior to any study-related procedures;
- Males and females aged from 2 years to 18 years and 11 months;
- Patients of any ethnic background were eligible for this study;
- Diagnosis of NPC, NPC1/NPC2;
- NPC diagnosis confirmed by
  - Genetically confirmed (deoxyribonucleic acid [DNA] sequence analysis) by mutations in both alleles of NPC1 or NPC2,

    OR
  - Mutation in only one allele of NPC1 or NPC2 plus either positive fillipin staining or elevated cholestane triol/oxysterols (>2 x upper limit of normal).
- Body mass index (BMI) Zscore- ≥-2 standard deviation (SD) for age, according to the World Health Organisation (WHO) standards;
- Presenting at least one neurological symptom of the disease (for example, but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia);
- Ability to walk either independently or with assistance;
- Ability to travel to the corresponding clinical study site repeatedly (every 6 months) for evaluation and follow up;
- Treated or non-treated with miglustat;
- If a patient was under prescribed treatment with miglustat, it had to be under stable[1] dose of the medication for ≥3 continuous months prior to inclusion in the study;
- Sexually active patients must have been willing and able to use an adequate method of contraception throughout the study, for example: diaphragm + spermicide; intrauterine contraceptive device; oral contraceptives; implant; injection of a

[1] Stable miglustat treatment was the recommended dose for the age of the patient, after the initial dose adjustment upon response and/or renal function integrity. A temporary dose reduction due to diarrhoea did not affect the concept of stable dose.

Name of Sponsor/Company: Orphazyme A/S	**Individual Study Table Referring to Part of the Dossier** **Volume** **Page**	**(For National Authority Use only)**
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

progestogen medication;

- Ability to comply with the protocol-specified procedures/evaluations and scheduled visits;
- Willing to participate in all aspects of study design including serial blood sampling, skin biopsies and imaging (ultrasonography) collections.

Exclusion criteria:

- No written informed consent obtained from the patient or their parent(s)/legal guardian(s) (and assent if appropriate to local laws and regulation) before any study related procedures;
- Recipient of a liver transplant or planned liver transplantation;
- Patients with uncontrolled severe epileptic seizures period2 (at least 3 consecutive severe epileptic seizures that required medication) within 2 months prior to the written consent. This includes patients with ongoing seizures that were not stable in frequency or type or duration over a 2 month period prior to enrolment, requiring change in dose of antiepileptic medication (other than adjustment for weight) over a 2 month period prior to enrolment, or requiring 3 or more antiepileptic medications to control seizures;
- Neurologically asymptomatic patients;
- Severe liver insufficiency (defined as hepatic laboratory parameters, aspartate transaminase [AST] and alanine transaminase [ALT] greater than three-times the upper limit of normal for age and gender;
- Severe renal insufficiency, with serum creatinine level greater than 1.5 times the upper limit of normal for age and gender;
- Severe manifestations of NPC disease that would interfere with the patient's ability to comply with the requirements of this protocol;
- In the opinion of the Investigator, the patient's clinical condition did not allow for the required blood collection and/or skin biopsies as per the protocol-specified procedures;

[2] An epileptic seizure is a transient symptom of abnormal excessive or synchronous neuronal activity in the brain. The outward effect can be as dramatic as a thrashing movement (tonic-clonic seizure) or as mild as a brief loss of awareness (absence seizure). It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. Sometimes it is not accompanied by convulsions but a full body slump, where the person simply will lose body control and slump to the ground. Seizures can occur in patients who do not have epilepsy. On the other hand, non-epileptic seizures are paroxysmal events that mimic an epileptic seizure but do not involve abnormal, rhythmic discharges of cortical neurons. These non-epileptic seizures are caused by either physiological or psychological conditions.

Name of Sponsor/Company: Orphazyme A/S	**Individual Study Table Referring to Part of the Dossier** **Volume** **Page**	**(For National Authority Use only)**
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

- Treatment with any investigational medicinal product (IMP) within 4 weeks prior to the study enrolment;
- Treatment with any IMP during the study in an attempt to treat NPC;
- Current participation in another study was not permitted unless it was a non-interventional study and the sole purpose of the study was for long-term follow-up/survival data (registry);
- Patients were excluded if there was a confirmed risk linked to the skin punch biopsy procedure like severe thrombocytopenia, at investigator's discretion.

Test Product, Dose and Mode of Administration, Batch Number, Duration of Treatment: Not applicable.

Criteria for Evaluation:

Safety parameters: AEs (disease related and treatment related), haematology, clinical chemistry, physical examination, vital signs and electrocardiogram (ECG).

Biomarker parameters: NPC1 protein, NPC1 protein function: cholesteryl esterification, oxysterols (cholestane-3β, 5α, 6β-triol and 7-ketocholeterol), un-esterified cholesterol and heat shock protein 70 (HSP70).

Imaging parameters: Changes in the size and/or characteristics of the liver and spleen (assessed by ultrasound).

Clinical status parameters: Clinical information collected in a prospective way:

A. NPC clinical status scores (NPC Clinical Severity Scale [NPCCSS] and "Stampfer" Score) were used to follow the general progression of NPC in:
   a) the patient population;
   b) as well as in every individual patient.
B. Quality of Life questionnaire was applied to the patients (and/or the patients' parent[s]/legal guardian[s]).

Retrospective historic clinical data was collected from the individual patient records.

Statistical Methods:

Continuous variables by descriptive statistics (number of patients [N], mean, SD, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %).

Name of Sponsor/Company: Orphazyme A/S	**Individual Study Table Referring to Part of the Dossier** **Volume** **Page**	**(For National Authority Use only)**
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

Summary of Results:

PATIENT DEMOGRAPHICS, DISEASE CHARACTERISTICS AND DISEASE PROGRESSION PROFILE SUMMARY

Demographics

Demographic characteristics were similar (except for gender) between the patients who used miglustat (n=30) and those who did not (n=6). Overall, the majority of patients were white (91.7%) and more than half were female (58.3%) with a mean BMI of 18.06 (SD=2.56). The overall mean age was 9.86 years (SD=4.61) with an age range from 2 to 18 years.

Disease Characteristics

All 36 patients (100%) had an NPC diagnosis of NPC1 and had a history of neurological symptoms. The majority of patients (30 [83.3%]) were treated with miglustat. The mean Niemann Pick type C clinical database (NPC-cdb) score (patient history) was 39.9 (SD=21.0; range: 4 to 91).

The mean time since first NPC symptom was 6.70 years (SD=3.70; range: 1.7 to 15.8 years); the mean time since disease confirmation by DNA test was 4.26 years (SD=3.06; range: 0 to 11.2 years)

The most common disease characteristics present per category in the patients' history included:

- Immunology history: Pneumonia (8/36 patients; 22.2%);
- Neurology (first neurological deficit at age): Impaired fine motor skills (32/36 patients; 88.9%);
- Cognitive abilities/behaviour/psychiatric symptoms: Supervision at home or at school needed (24/36 patients; 66.7%);
- Speech/hearing: Dysarthria (single words inarticulate) (31/36 patients; 86.1%);
- Daily routines: Diarrhoea (21/36 patients; 58.3%);
- Eating and drinking: Dysphagia (13/36 patients; 36.1%).

Patient Disease Progression Profile

NPCCSS

The mean total NPCCSS score at Visit 1 was 16.7 (SD=9.6). There was a mean increase of 2.7 (SD=4.0) to Visit 2 at which the mean total NPCCSS score was 18.6 (SD=10.7).

The mean rate of change in the NPCCSS total score (all sub-domains) per 6 months was 1.47 (SD=2.25; range: -2.9 to 8.5).

NPCCSS (Total Score for 5 Key Sub-domains)

The mean total NPCCSS score for the 5 key sub-domains (ambulation, speech, swallow, cognition and fine motor skills) at Visit 1 was 9.6 (SD=6.0). There was a mean increase of 1.4 (SD=2.9) to Visit 2 at which the mean total NPCCSS score for the 5 key sub-domains was 10.7 (SD=6.6).

The mean rate of change in the NPCCSS total score for the 5 key sub-domains per 6 months was 0.75 (SD=1.58; range: -2.3 to 6.6).

NPCCSS (Ambulation)

The mean NPCCSS score for ambulation at Visit 1 was 2.0 (SD=1.5). There was a mean increase of 0.3 (SD=0.7) to Visit 2 at which the mean NPCCSS score for ambulation was 2.2 (SD=1.7).

NPCCSS (Speech)

The mean NPCCSS score for speech at Visit 1 was 1.6 (SD=1.2). There was a mean increase of 0.3 (SD=0.9) to Visit 2 at which the mean NPCCSS score for speech was 2.0 (SD=1.4).

NPCCSS (Swallow)

The mean NPCCSS score for swallow at Visit 1 was 1.2 (SD=1.7). There was a mean increase of 0.4 (SD=0.9) to Visit 2 at which the mean NPCCSS score for swallowing was 1.4 (SD=1.8).

NPCCSS (Cognition)

The mean NPCCSS score for cognition at Visit 1 was 2.7 (SD=1.3). The mean change in NPCCSS score for cognition from Visit 1 to Visit 2 was 0 (SD=0.6); the mean NPCCSS score for cognition at Visit 2 was 2.7 (SD=1.4).

NPCCSS (Fine Motor Skills)

The mean NPCCSS score for fine motor skills at Visit 1 was 2.0 (SD=1.6). There was a mean increase of 0.4 (SD=1.1) to Visit 2 at which the mean NPCCSS score for fine motor skills was 2.5 (SD=1.8).

NPCCSS (All Other Sub-domains)

The mean total NPCCSS score for all other sub-domains (eye movement, hearing, memory, seizures, gelastic cataplexy, hyperreflexia, narcolepsy, incontinence, behaviour, auditory brainstem response, psychiatric and respiratory) at Visit 1 was 7.1 (SD=4.4). There was a

Name of Sponsor/Company: Orphazyme A/S	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Not applicable	Volume	
Name of Active Ingredient: Not applicable	Page	

mean increase of 1.2 (SD=2.1) to Visit 2 at which the mean total NPCCSS score for all other sub-domains was 7.9 (SD=5.0).

The NPCCSS score for sub-domain hyperreflexia showed a mean decrease of 0.1 (SD=0.8) from Visit 1 to Visit 2. There was no mean change in the NPCCSS scores for subdomains hearing, gelastic cataplexy, auditory brainstem response and respiratory from Visit 1 to Visit 2. All other sub-domain NPCCSS scores, showed minimal mean increase from Visit 1 to Visit 2.

The mean rate of change in the NPCCSS total score for all other sub-domains per 6 months was 0.72 (SD=1.36; range: -2.0 to 5.3).

NPC-cdb Score

The mean total NPC-cdb score at Visit 1 was 39.4 (SD=20.0). There was a mean increase of 5.0 (SD=7.9) to Visit 2 at which the mean total NPC-cdb score was 42.8 (SD=21.8).

NPC-cdb Score (Epilepsy Sub-domain)

The mean total NPC-cdb score for epilepsy sub-domain (seizures/cataplexy/narcolepsy) at Visit 1 was 2.6 (SD=3.0). There was a mean increase of 0.2 (SD=1.9) to Visit 2 at which the mean total NPC-cdb score for epilepsy sub-domain was 2.7 (SD=3.1).

Quality of Life

In terms of mobility, the majority of patients (22/36 patients; 61.1%) experienced some or high level of problems walking around at Visit 1. Approximately the same ratio of patients (19/30 patients; 63.3%) reported these problems at Visit 2.

In terms of self-care, most patients experienced some or high level of problems with washing or dressing themselves at Visit 1 (30/35; 85.7%). At Visit 2, a slightly lower proportion reported this type of problems (23/30; 76.7%).

In terms of the ability to undertake usual activities, the majority of patients (24/36 patients; 66.7%) experienced problems at Visit 1. At Visit 2 there was a slight reduction (18/31 patients; 58.1%).

In terms of pain or discomfort, only a small group of patients experienced some pain or discomfort at Visit 1 (8/35 patients; 22.9%). This proportion was doubled at Visit 2 (13/31 patients; 41.9%).

The assessment of the patient's health according to the VAS showed a mean change of -4.0 (SD=18.6) from Visit 1 (mean score of 68.8 [SD=19.9]) to Visit 2 (mean score of 64.4 [SD=21.2]).

Name of Sponsor/Company: Orphazyme A/S	Individual Study Table Referring to Part of the Dossier Volume Page	(For National Authority Use only)
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

In terms of feeling anxiety or depressed, approximately one third of the patient population reported some level of anxiety/depression (11/36 patients; 30.6%). This proportion increased at Visit 2 (13/31 patients; 41.9%).

The change in the individual EQ-5D-Y items per patient as classified according to the Pareto principles (categorised in 4 overall groups [worse/better/same/mixed]) showed that 23% of the patients felt better at Visit 2, 40% felt worse, 13% showed a mixed result with improvements in some domains and decline in others, and 23% of the patients experienced no change at Visit 2.

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Biomarkers

The mean result for cholesteryl esterification at Visit 1 was 462.14 ng/mg (SD=283.60). There was a mean increase of 122.37 ng/mg protein (SD=474.04) to Visit 2 at which the mean result for cholesteryl esterification was 616.89 ng/mg (SD=443.10).

The mean result for serum cholestane-triol (oxysterols) at Visit 1 was 88.31 ng/mL (SD=28.66). There was a mean increase of 3.52 ng/mL (SD=14.92) to Visit 2 at which the mean result for serum cholestane-triol (oxysterols) was 88.52 ng/mL (SD=31.56).

The mean result for PBMC un-esterified cholesterol at Visit 1 was 77556.7 ng/mg protein (SD=21528.3). There was a mean increase of 28056.5 ng/mg protein (SD=108522.2) to Visit 2 at which the mean result for PBMC un-esterified cholesterol was 98453.6 ng/mg protein (SD=99561.3).

The mean result for skin un-esterified cholesterol at Visit 1 was 2.793 µg/mg of skin (SD=0.959). There was a mean decrease of 0.372 µg/mg of skin (SD=0.842) to Visit 2 at which the mean result for skin un-esterified cholesterol was 1.891 (SD=0.644).

The mean rates of change per 6 months were as follows:

- Cholesteryl esterification: 57.41 ng/mg (SD=303.81; range: -563.6 to 625.4 ng/mg);
- Serum cholestane-triol (oxysterols): 2.64 ng/mg protein (SD=10.69; range: -17.1 to 36.3 ng/mg protein);
- PBMC un-esterified cholesterol: 25943.72 ng/mg protein (SD=97557.45; range: -20545.3 to 440908.9 ng/mg protein);

Name of Sponsor/Company: Orphazyme A/S	Individual Study Table Referring to Part of the Dossier Volume Page	(For National Authority Use only)
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

- Skin un-esterified cholesterol: -0.23 µg/mg of skin (SD=0.47; range: -0.8 to 0.4 µg/mg of skin).

Imaging

The mean liver size at Visit 1 was 131.8 mm (SD=19.3). There was a mean decrease of 1.2 mm (SD=14.5) to Visit 2 at which the mean liver size was 130.0 mm (SD=23.3).

The mean spleen size at Visit 1 was 138.6 mm (SD=26.0). There was a mean increase of 5.0 mm (SD=13.0) to Visit 2 which had the mean spleen size was 141.8 mm (SD=23.8).

SAFETY

Study Termination

In total, 31 patients (86.1%) completed the study. Five (5) patients (13.9%) withdrew early from the study due to the following reasons: 1 patient had a protocol violation and withdrew after 72 days, 1 patient was lost to follow up after 152 days and 3 patients had the reason recorded as 'other' for early study termination and withdrew after 162 days (reason: moved to USA), 401 days (reason: discontinued due to deterioration) and 120 days (reason: unknown), respectively.

Adverse Events

A total of 120 AEs were reported in 25 (69.4%) of the 36 patients enrolled in the study.

The system organ classes (SOCs) in which most AEs were reported were infections and infestations (49 AEs in 18 patients [50.0%]), gastrointestinal disorders (29 AEs in 10 patients [27.8%]) and general disorders and administration site conditions (9 AEs in 9 patients [25.0%]). The most common AEs occurring in only equal or above 10.0% of patients were rhinitis (8 patients [22.2%]), diarrhoea (7 patients [19.4%]), pyrexia (6 patients [16.7%]) and nasopharyngitis (5 patients [13.9%]).

The majority of events (63/120 AEs [52.5%]) were mild (CTCAE Grade 1); 47/120 AEs (39.17%) were moderate (CTCAE Grade 2).

Ten (10) AEs in 5 patients (13.9%) were considered severe (CTCAE Grade 3); these events were: infection of circumcision operation site, percutaneous endoscopic gastrostomy (PEG) site infection, pharyngitis; scarlet fever, pneumonia, ear infection, Epstein-Barr Virus infection, circumcision, AST increased and diarrhoea. The majority of severe AEs were not related to NPC disease, any study procedures or disease-related medicinal products given. One (1) severe AE (diarrhoea) was considered definitely related to miglustat.

Overall, 3 patients (8.3%) had 5 events (all CTCAE Grade 3 in severity; all recovered/resolved) that were serious adverse events (SAEs): 2 instances of infection, 1 case

Name of Sponsor/Company: Orphazyme A/S	Individual Study Table Referring to Part of the Dossier Volume Page	(For National Authority Use only)
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

of pharyngitis, 1 case of scarlet fever and an Epstein–Barr virus infection. None of these events were considered to be related to NPC disease, related to medicinal products given, or related to study procedures.

Ten (10) of the 120 AEs were considered definitely related to NPC disease, whilst 1 event was regarded as probably related, 9 events as possibly related and another 9 events unlikely related to the NPC disease. All other events (91 AEs) were considered not related to NPC disease.

Events recorded as definitely related to NPC disease were:

- Concussion, epilepsy, splenomegaly, joint dislocation, minor cognitive motor disorder, cataplexy and speech disorder in 1 patient each and hepatomegaly for 2 patients.

The 1 event recorded as probably related to NPC disease was thrombocytopenia.

Events recorded as possibly related to NPC disease included:

- Pain, congenital scoliosis, abdominal pain, malaise, pain in extremity, bronchitis and rhinitis in 1 patient each and diarrhoea for 2 patients.

In total, 1 patient had 8 AEs (all cases of diarrhoea) that were considered definitely related to disease-related therapy (miglustat). One (1) patient had an AE (skin infection) that was considered probably related to a study procedure (skin biopsies).

There were no AEs leading to withdrawal in this study. No patients died during this study.

Laboratory Evaluations, Vital Signs, Physical Examination, Electrocardiogram

The majority of haematology and clinical chemistry laboratory results were normal during the study (Visit 1 to Visit 2). There were no significant overall trends or changes in the laboratory data over time.

Four (4) patients had abnormal haematology results considered clinically significant during the study: Visit 1 (2 patients) and Visit 2 (4 patients) (2 patients had clinically significant haematology results at both Visit 1 and Visit 2).

One (1) clinically significant haematology result was documented as an AE:

- Visit 2 platelet count of 90 GI/L (reference range: 130 – 394 GI/L) documented as CTCAE Grade 1 thrombocytopenia.

Five (5) patients had abnormal clinical chemistry results considered clinically significant during the study: Visit 1 (3 patients) and Visit 2 (3 patients) (1 patient had clinically

Name of Sponsor/Company: Orphazyme A/S	Individual Study Table Referring to Part of the Dossier Volume Page	(For National Authority Use only)
Name of Finished Product: Not applicable		
Name of Active Ingredient: Not applicable		

significant clinical chemistry results at both Visit 1 and Visit 2).

One (1) clinically significant abnormal clinical chemistry result was documented as an AE:

- Visit 2 (EoS) AST 106 U/L (reference range: 10 – 40 U/L) documented as CTCAE Grade 3 AST increased.

There was little change in vital signs during the study from Visit 1 to Visit 2. There were no individual changes in vital signs of clinical relevance.

In total, 31 patients (86.11%) had abnormal physical examination findings during the study; In 23 patients (63.9%) the findings were considered clinically significant.

The most common abnormal physical examination findings were in the central nervous system (CNS) (29 patients [82.9%] at Visit 1; 26 patients [81.3%] at Visit 2) and abdomen (18 patients [51.4%] at Visit 1; 16 patients [50%] at Visit 2).

Although there were some changes in physical examination findings between Visits 1 and 2, no patient had a change in examination findings showing a significant deterioration in their condition.

The majority of the ECGs were recorded as normal; no clinically significant abnormal ECG findings were reported in this study.

OVERALL CONCLUSION

The data from the CT-ORZY-NPC-001 study supports the characterization of NPC as a severe neurological disease with a progression course that is slow in the majority of the patients. The slow disease progression highlights the importance of a long observation period in a clinical study setting. The biomarker analyses supports the use of cholestane triol, cholesterol esterification rate and un-esterified cholesterol, measured in skin biopsies, as potential biomarkers of NPC. The collected safety data are in line with those expected in the NPC population.

Date of the Report:
01 May 2018