

ARIMOCLOMOL COMPOSITIONS FOR USE IN TREATING NIEMANN PICK
DISEASE TYPE C (NPC)

STATEMENT OF RELATED APPLICATIONS

This application is a conversion of U.S. Provisional Patent Application 63/419,985, filed on October 27, 2022, and claims priority to that date, and incorporates by reference all materials thereof herein.

BACKGROUND OF THE INVENTION

[001] Niemann-Pick disease type C (NPC) is a rare, progressive, and fatal neurodegenerative disorder with an estimated incidence of ~1:100,000 live births (Geberhiwot et al. 2018). It is characterized by gradual loss of function that typically leads to death before adulthood. Overall, the mean life expectancy for patients with NPC is 13 years (Bianconi et al. 2019). It has substantial impact on all aspects of the life of the patients and their families.

[002] The disease is characterized by a range of progressive and disabling symptoms including increasing difficulties with basic functions such as walking, motor coordination, swallowing, speaking, concentrating and remembering, leading to complete dependency on family and caregivers.

[003] NPC is an autosomal recessive disorder caused by mutations in the NPC1 (95% of cases) or NPC2 genes. Both genes encode lysosomal proteins that are essential in intracellular transport and metabolism of lipids. As a result of the mutations, NPC proteins are often misfolded and degraded prematurely, causing dysfunction of either one or both of the NPC proteins. As a result of the dysfunction of either of these NPC proteins, lysosomal function is impaired causing an accumulation of lipids in the lysosomes, which in turn leads to cell stress and toxicity (Lloyd-Evans and Platt 2010; Platt et al. 2018). Over time, this leads to neurodegeneration as well as peripheral organ dysfunction. Liver, spleen, and lungs may be affected as well. The

age of onset for NPC disease can vary greatly, from a neonatal rapidly progressive fatal disorder to an adult-onset slowly progressing neurodegenerative disease.

[004] The disease is characterized by a range of progressive and disabling symptoms including increasing difficulties with basic functions such as walking, motor coordination, swallowing, speaking, concentrating and remembering, leading to complete dependency on family and caregivers (Wraith and Imrie 2007). The progressive deterioration of brain function leads to a significant decrease in the quality of life of patients and their families (Benussi et al. 2018).

[005] While manifesting most commonly during childhood and adolescence, NPC can present at any stage of life with highly diverse symptomatology and with variable speed and patterns of progression – from a neonatal, rapidly progressive fatal disorder, to an adult-onset, slowly progressing, neurodegenerative disease. NPC can be categorized by age of neurological symptoms: early infantile (onset before age 2), late infantile (onset between ages 2 and 6), juvenile (onset between ages 6 and 15), and adult (onset after age 15). The disease progression largely correlates with the age of onset of the neurologic symptoms. Earlier age of onset for neurological signs and symptoms is also predictive of rapid disease progression. Double functional null NPC1 genotype predicts an early infantile and severe NPC. No single symptom can predict the progression rate of the individual patient (Vanier 2010; Yanjanin et al. 2010).

[006] Systemic signs of liver, spleen and lung involvement typically precede the disease-defining neurodegeneration. This is particularly true for patients with onset during infancy and childhood. Neurological signs and symptoms include ambulation and walking difficulties, cognitive impairment, swallowing difficulties, vertical supranuclear gaze palsy, seizures, and ataxia. The progression of the neurological symptoms is responsible for disability and premature death in most cases (Vanier 2010).

[007] The high variability of most signs and symptoms of NPC, combined with little or no experience with the disease among clinicians, leads to substantial diagnostic delays, misdiagnoses, and delayed intervention. However, in cases where

the disease has been confirmed in one child, the sibling can be diagnosed with NPC by genetic testing before the onset of any visible signs or symptoms.

[008] At the terminal stage, patients are bedridden with complete ophthalmoplegia and loss of volitional movements caused by severe encephalopathy with uncontrolled seizures. At this stage, therapy consist primarily of palliative care.

[009] While Miglustat is authorized in the European Union (EU) for the treatment of progressive neurological manifestations in patients with NPC, at present there are no cure or disease-modifying therapies for NPC. Consequently there is a high unmet medical need for new treatment options (Geberhiwot et al. 2018). Given the progressive, debilitating, life limiting, and fatal nature of the NPC disease (i.e., high morbidity), there is an urgent need for treatments that delay disease progression, as patients continuing to have progressive neurodegeneration with fatal outcome. In a recent paper over an observation period of 50 years, 338 deaths caused by NPC with a mean age of 13 years were described and it was concluded that there was no significant change in survival over the last 20 years (Bianconi et al. 2019).

[010] Since at present there are no cure or disease-modifying therapies for NPC, and consequently there is a high unmet medical need for new treatment options (Geberhiwot et al. 2018). Given the progressive, debilitating, life limiting, and fatal nature of the NPC disease (i.e., high morbidity), there is an urgent need for treatments that delay disease progression, such as the present disclosure monotherapy treatment of arimoclomol citrate or in combination therapy with miglustat. There is also a present need to provide improved delivery and administration of arimoclomol medicaments, to enhance patient compliance with such administration, especially with patients aged 2 years or less.

BRIEF SUMMARY OF THE INVENTION

[011] The present disclosure further relates to one or more methods of treating NPC in a human patient, comprising a pharmaceutical composition or formulation of arimoclomol citrate or a pharmaceutically acceptable salt thereof, either in monotherapy or in combination treatment therapy with miglustat. The present disclosure additionally relates to methods of treating NPC in a human patient via

dispersion or suspension of a pharmaceutical composition comprising a formulation of arimoclomol, specifically arimoclomol citrate, in at least one liquid or at least one solid medium prior to administration to the patient. The present disclosure further relates to the biomarkers and metabolites of arimoclomol.

[012] MIPLYFFA®, a arimoclomol citrate formulation, is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 years and older, in combination with miglustat and as monotherapy in patients not suitable for therapy with miglustat.

[013] In at least one aspect of the disclosure, this disclosure provides a method of treating Niemann Pick disease, type C (NPC), in a human patient in need thereof, the method comprising the steps of: providing to the patient a sufficient amount of a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof; wherein the composition or formulation of arimoclomol is provided in a capsular dosage form; and wherein the sufficient amount of the pharmaceutical composition or formulation of arimoclomol, or the pharmaceutically acceptable salt thereof, is selected from the group consisting of 31 mg, 47mg, 62mg, 93mg, and 124mg of arimoclomol (base form); opening the capsular dosage form and dispersing the pharmaceutical composition or formulation of arimoclomol or the pharmaceutically acceptable salt thereof in at least one liquid or at least one solid medium to form at least one dispersion; wherein the liquid medium is at least one member selected from the group consisting of water and apple juice; wherein the solid medium is selected from the group consisting of at least one soft food; and administering the dispersion to the patient within a twenty-four period of time after the pharmaceutical composition or formulation, or the pharmaceutically acceptable salt thereof, is dispersed within the at least one liquid or solid medium.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[014] FIG. 1 are chemical drawings that show the metabolization of arimoclomol.

[015] FIG. 2 is Table 41, entitled Comparison of test data obtained from vessel 1-6 vs. vessel 7-12.

[016] FIG. 3 is entitled Figure 2-3, depicting a graph showing mean plasma concentrations of arimoclomol and its metabolites M2, M5, and M105 following multiple-doses of 248 mg three times a day (t.i.d.) – Trial OR-ARI-MET-01.

[017] FIG. 4 is Table 2-5, entitled Single and Multiple dose Pharmacokinetic Parameters of arimoclomol metabolites M2, M5, and M105 in male subjects – Trial OR-ARI-MET-01.

[018] FIG. 5 is Table 11-2, entitled Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Therapeutic Dose (200 mg) of Arimoclomol TID (Treatment A) on Days 1 and 3.

[019] FIG. 6 is Table 11-5, entitled Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Supratherapeutic Dose (600 mg) of Arimoclomol TID (Treatment B) on Days 1 and 3.

[020] FIG. 7 is Table 11-3, entitled Summary Statistics of Plasma Pharmacokinetic Parameters of M105 Following the Therapeutic Dose (200 mg) of Arimoclomol TID (Treatment A) on Days 1 and 3.

[021] FIG. 8 is Table 11-6, entitled Summary Statistics of Plasma Pharmacokinetic Parameters of M2 Following the Supratherapeutic Dose (600 mg) of Arimoclomol TID (Treatment B) on Days 1 and 3.

[022] FIG. 9 is Table 3-4, entitled Dose Proportionality of Arimoclomol Following Multiple t.i.d. Administration.

[023] FIG. 10 12 is Table 3-3, entitled Arimoclomol Oral Clearance Following Single Dosing and Multiple t.i.d. Oral Dosing of 31 to 372 mg.

[024] FIG. 11 is Table 2-10, entitled Summary Statistics of arimoclomol exposure variables stratified by body weight band.

[025] FIG. 12 is entitled Figure 3-6 and depicts a table comparison showing the Impact on Hepatic impairment in the single-dose pharmacokinetics of arimoclomol – Trials OR-ARI-HEP-01.

[026] FIG. 13 is Table 6-6 and is entitled Intrinsic Factor Pharmacokinetic Trials of 248 mg dosages for various hepatic conditions and resultant AUC and Cmax.

[027] FIG. 14 is entitled Figure 3-4 and shows the impact of age, sex, and weight on the multiple dose pharmacokinetics of arimoclomol – population pharmacokinetic analysis in adults, Cmax (top) AUC0-8 (bottom).

[028] FIG. 15 is a chart showing estimated change from baseline to Month 36 in 5-domain NPCCSS for double-blind and open-label arimoclomol.

[029] FIG. 16 is a table comparison showing p-values for arimoclomol vs placebo for full population and subgroup with use of miglustat at baseline.

[030] FIG. 17 is entitled Figure 2-17 and depicts analysis of change from baseline to Month 12 in 5-domain and full-scale NPCCSS in subgroups based on age at first neurological symptom (FAS).

DETAILED DESCRIPTION OF THE INVENTION

[031] The present disclosure relates to one or more methods of treating NPC in a human patient, comprising a pharmaceutical composition or formulation of arimoclomol citrate or a pharmaceutically acceptable salt thereof, either in monotherapy or in combination treatment therapy with miglustat. The present disclosure additionally relates to methods of treating NPC in a human patient via dispersion or suspension of a pharmaceutical composition or formulation of arimoclomol, specifically arimoclomol citrate, in at least one liquid or at least one solid medium prior to administration to the patient. The present disclosure further relates to the biomarkers and metabolites of arimoclomol.

[032] Arimoclomol citrate capsules are available in five strengths expressed as arimoclomol base: 31 mg, 47 mg, 62 mg, 93 mg and 124 mg. It is easy to administer to patients with swallowing difficulties, including pediatric patients, as it is formulated in a capsule that can be opened and the contents can be dispersed in liquid, such as but not limited to apple juice or similar beverage, or soft food (e.g., applesauce, gelatin, baby food, among others for use with neonatal, pediatric, and other patients requiring such soft mediums), without any significant or potentially significant loss of potency

for at least 24 hours. In one embodiment of the disclosure, the content of the arimoclomol citrate capsule can be easily suspended in 20 mL water to be administered through a feeding tube or, alternatively, can be sprinkled on soft food and beverages with different texture, viscosity and pH, without any loss of potency for at least 24 hours.

[033] Arimoclomol citrate (N-[(2R,Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrate) is a synthetic chemical entity, also known as BRX-345. Arimoclomol is a heat shock protein amplifier.

[034] In at least one embodiment of the present disclosure, a method of treating NPC in a patient is presented, wherein the treatment comprises administering arimoclomol citrate to the patient in need thereof. In one or more alternative embodiment, the patient in need thereof is aged 2 or older, or alternatively aged 2 or less. In another embodiment, the treatment is a monotherapy treatment with arimoclomol (for example, MIPLYFFA ©) only, especially wherein the patient is not suitable for treatment with miglustat. Yet in another embodiment, the treatment additionally comprises administering miglustat to the patient in need thereof.

[035] In a further embodiment of the present disclosure, a method of treating NPC in a patient is presented, wherein the treatment comprises administering arimoclomol citrate to the patient in need thereof, wherein a dosage amount is selected from the group consisting of 31 mg, 47 mg, 62 mg, 93 mg and 124 mg of arimoclomol (base). In an alternative embodiment, the patient in need thereof is aged 2 or older, or alternatively aged 2 or less. In another embodiment, the treatment is a monotherapy treatment with arimoclomol (MIPLYFFA ©) only, especially wherein the patient is not suitable for treatment with miglustat. Yet in another embodiment, the treatment additionally comprises administering miglustat to the patient in need thereof.

[036] In a still further embodiment of the present disclosure, a method of treating NPC in a patient is presented, wherein the treatment comprises administering arimoclomol citrate to the patient in need thereof, wherein the mode of administration may be oral, for example, via a capsule, or the capsule may be open and disbursed in liquid (e.g., a suspension) or soft food (e.g., applesauce, gelatin, baby food, among

others for use with neonatal, pediatric, and other patients requiring such soft mediums). In an alternative embodiment, the patient in need thereof is aged 2 or older, or alternatively aged 2 or less. In another embodiment, the treatment is a monotherapy treatment with arimoclomol (MIPLYFFA ©) only, especially wherein the patient is not suitable for treatment with miglustat. Yet in another embodiment, the treatment additionally comprises administering miglustat to the patient in need thereof.

[037] In another embodiment of the present disclosure, one or more metabolites of arimoclomol citrate are presented. In one embodiment, the one or more metabolites are selected from the group consisting of M2, M5 and M105.

[038] In one embodiment, the present disclosure concerns the use of arimoclomol citrate for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 and older, or alternatively aged 2 or less, either as a monotherapy or as a combination therapy with miglustat.

[039] In an alternative embodiment, MIPLYFFA©, an arimoclomol citrate formulation, is indicated for the treatment of Niemann-Pick disease type C (NPC) in patients aged 2 and older, in combination with miglustat and as monotherapy in patients not suitable for therapy with miglustat.

Mode of action

[040] Without wishing to be bound by a particular belief, it is believed that Arimoclomol is an orally available small molecule that crosses the blood brain barrier (BBB) (Cudkowicz et al. 2008). Arimoclomol amplifies and sustains the cellular production of heat shock proteins (HSPs), in particular, HSP70, through prolonged activation of heat shock factor-1 (HSF-1), and induction of the HSR (Kalmar et al. 2008; Neef, Jaeger, and Thiele 2011). HSP70 and other HSPs are critical to correct folding and processing of the integral lysosomal membrane protein NPC1, including misfolding mutations, which is the most common form of mutated NPC1 in patients suffering from NPC (Nakasone et al. 2014; Millat et al. 2001). The HSR is linked directly to lysosomal integrity through HSP70 mediated stabilization of lysosomal membranes and protection from cell death (Kirkegaard et al. 2010; Petersen et al.

2010; Nylandsted et al. 2004). Thus, by amplifying the HSR, arimoclomol targets both protein misfolding and lysosomal dysfunction through a natural cellular defense mechanism. Arimoclomol therefore has a novel mechanism of action targeting the fundamentals of NPC etiology: NPC protein misfolding and lysosomal dysfunction (Ingemann and Kirkegaard 2014; Neef, Jaeger, and Thiele 2011; Kirkegaard et al. 2016).

[041] In one embodiment of the present disclosure, the finished product is presented as capsules, hard containing 31, 47, 62, 93 or 124 mg respectively of arimoclomol citrate as active substance (base). In one embodiment, other inert ingredients may include microcrystalline cellulose and magnesium stearate (as part of capsular contents).

[042] In one embodiment of the present disclosure, the arimoclomol citrate (MIPLYFFA®) capsule shells:

[043] MIPLYFFA® 31 mg: hypromellose, titanium dioxide, brilliant blue FCF-FD&C Blue 1;

[044] MIPLYFFA® 47 mg: hypromellose, titanium dioxide, brilliant blue FCF-FD&C Blue 1, yellow iron oxide;

[045] MIPLYFFA® 62 mg: hypromellose, titanium dioxide, yellow iron oxide;

[046] MIPLYFFA® 93 mg: hypromellose, titanium dioxide, yellow iron oxide, red iron oxide;

[047] MIPLYFFA® 124 mg: hypromellose, titanium dioxide, red iron oxide.

[048] Printing ink: shellac, black iron oxide, propylene glycol, ammonia, potassium hydroxide.

Active Substance

[049] Arimoclomol is a chiral molecule containing one chiral center (R-enantiomeric form) and is provided as a white to off-white crystalline powder. Arimoclomol citrate (N-[(2R,Z)-2-hydroxy-3-(1-piperidyl)propoxy]pyridine-3-carboximidoyl chloride, 1-oxide, citrate) is a synthetic chemical entity. It is highlighted

that it is slightly hygroscopic, presented as the R-enantiomeric form and consistently observed in polymorph form 1.

Pharmacology

[050] Niemann-Pick disease type C (NPC) belongs to the larger group of diseases known as lysosomal storage disorders (Platt et al., 2018). NPC is a rare progressive autosomal recessive genetic disorder characterized by an inability of the body to transport cholesterol and other sphingolipids inside of cells. NPC is caused by mutations in the NPC1 gene (NPC type 1C in 95%) or the NPC2 gene (NPC type 2C, in 5%), which are both lipid transporters located in the lysosomes. As a consequence of this genetic disorder, abnormal accumulation of lipids are observed in the lysosomes and retention of mutated NPC1 protein in the endoplasmic reticulum. These accumulations lead to enhanced degenerative processes like autophagy and cell death. Patients suffer from these degenerative processes predominantly in the central nervous system, liver, spleen and lung.

[051] Arimoclomol is an orally available small molecule intended to be administrated to NPC patients aged 2 and older, or alternatively aged 2 or less. Depending on age and weight of the patients the proposed arimoclomol dose (arimoclomol base, arimoclomol citrate) varies from 31 mg to 124 mg and should be given three times a day with or without food.

[052] Without wishing to be bound by any particular theory, the rationale for arimoclomol administration is based on observations that expression of the transcription factor HSF1 is enhanced, leading to the induction of the heat shock response (HSR), HSP70 and mature NPC1 protein. Thereby, the application of arimoclomol should lead to stabilization of the lysosomal integrity and restoration of misfolded NPC1 mutations in Niemann-Pick Type C disease.

[053] The exact target mechanism for arimoclomol is unknown. However, application of up to 400 μ M arimoclomol significantly increased HSF1, HSP70 and the NPC1 cholesterol transporter in human fibroblasts from NPC1 patients (but not below 100 μ M). Taken together, a concentration of 400 μ M arimoclomol is considered to

significantly enhance the heat shock response and processing of mature glycosylated NPC1 proteins.

[054] The three most abundant arimoclomol metabolites in humans at steady state (M2, M5 and M105) were ineffective with respect to the induction of HSP70 and enhancement of NPC1 protein levels in human fibroblast cells from NPC1 patients.

[055] Arimoclomol was also investigated in vivo in an NPC^{-/-} mouse model. The animal model mimics the impairments of NPC disease and is therefore considered suitable to evaluate efficacy of arimoclomol. Importantly, 30 mg/kg arimoclomol significantly enhanced the overall survival of NPC^{-/-} mice (Kirkegaard et al. 2016). Arimoclomol was orally applied in daily doses of 1-300 mg/kg (Kirkegaard et al. 2016; study no. CRO-1211210031). While data within the publication Kirkegaard et al. are consistent, this is not the case if including the data from study no. CRO-1211210031 (Kirkegaard et al. 2016).

[056] Although not wishing to be bound by any particular theory, the effect of arimoclomol in Npc1^{-/-} mice provides evidence that arimoclomol targets NPC etiology. Arimoclomol (10 mg/kg orally) significantly activates HSF1 and augments HSP70 protein levels in brains, but not in liver tissue of Npc1^{-/-} mice, which may be due to different expression of HSF1 and nuclear turnover in this tissue.

[057] Arimoclomol was shown to improve gait parameters in the absence of NPC1 protein. It is suggested that arimoclomol activates HSF1 and increases levels of HSP70 which in turn improve lysosomal function within the CNS, reduce lipid storage, and improve myelination and preservation of cerebellar structures. This provides an alternative mechanism of action of arimoclomol in the absence of NPC1 protein and supports the improved locomotion results in mice.

Pharmacokinetics

[058] Study 7027-130 strived to identify whether human cytochrome P450 isoenzymes are involved in the in vitro metabolism of radiolabeled arimoclomol in human microsomes (NADPH used as cofactor). In vivo metabolism (as well as absorption and excretion) of radiolabeled arimoclomol after oral administration (375

mg/kg salt) was then studied in intact and bile duct cannulated 6 to 9 weeks old male rats (Study 7027-122). Similarly, absorption, metabolism and excretion of radiolabeled arimoclomol was studied after oral administration (70 mg/kg) in intact and bile duct cannulated female and male Beagle dogs (Study 7027-124). Then, in the early study BRX-345 PRE SK-006, metabolites from rat and human specimens were identified and characterized based on liquid chromatographic separation coupled to mass spectrometry (MS). In the later study 287N-0801 part 2, metabolites were identified and profiled in plasma, urine and feces after oral administration of radiolabeled arimoclomol (2500 mg/kg) to male CD-1 mice (specimens were collected from study 287N-0801 part 1). Subsequently, in study XT194101, the Applicant investigated which (recombinant) UDP-glucuronosyltransferases are involved in the in vitro turnover of arimoclomol into the glucuronic acid conjugate metabolite M5 in human microsomes. In study XT194103, the Applicant attempted to investigate the metabolic pathways converting arimoclomol to the important cleavage product metabolite M105 in human microsomes (NADPH as cofactor), especially emphasizing on the role of (recombinant) flavin-containing monooxygenases (FMO). Later, in study 8384372, absorption and metabolism of radiolabeled arimoclomol (375 mg/kg) after oral gavage administration was studied in male rats. Furthermore, metabolism and speciation of arimoclomol-related material in plasma after repeated dose administration (for 28 days, specimens obtained from the rat fertility study 8376167), was also assessed in this study. Also, human metabolism studies were submitted in the dossier. In study 8393986, the Applicant characterized the plasma metabolites of arimoclomol after repeated administration for up to six days (at 400 mg thrice a day, at 8 h dose intervals) by LC-MS/MS at steady-state (samples obtained from clinical study 180308-CS030, sponsor reference: OR ARI-MET-01). In data report 8412783, additional data to study 8393986 was presented.

[059] Phase I metabolism of arimoclomol by CYP450 monooxygenases was inefficient, only the isoforms 1A2 and, more extensively, 2D6 were demonstrated to metabolize arimoclomol, but CYP450-mediated metabolism was quantitatively negligible to other turnover routes. Arimoclomol is metabolized by several routes, as demonstrated in FIG. 1 below:

[060] Primary routes of arimoclomol metabolism are a.) de-chlorination with subsequent glutathione conjugation and derivatization of the conjugate moiety; b.) O-glucuronidation; and c.) NO-cleavage. The most abundant metabolites produced by these reactions at steady state in animals and humans are M2 (cysteine conjugate), M5 (O-glucuronide) and M105 (cleavage product). The Applicant demonstrated that different UDP-glucuronosyl transferase isoforms (specifically UGT1A3, 1A9, 2B4, 2B7 and 2B17) can transform arimoclomol to M5 in human microsomes in vitro. The exact molecular mechanisms behind the NO-cleavage were not determined; however, FMO1 and FMO3 were demonstrated in vitro to potentially form M105 out of the intermediate 104 (and M109 out of arimoclomol). The Applicant did however not succeed to elucidate the metabolic pathways leading to M104. Metabolism was very similar between the tested non-clinical species and humans. The main metabolites in human plasma (>10%: M2, M5 and M105) were sufficiently present during non-clinical animal studies; their safety profile can therefore be considered as qualified.

[061] As discussed before, the speciation of arimoclomol-related material in plasma is different after chronic administration as compared to after single administration, whereby the fraction of arimoclomol metabolites of the total plasma amount of arimoclomol-related material considerably increases after chronic administration (because of their slower elimination kinetics).

Bioanalytical methods

Bioequivalence

[062] A BCS-based biowaiver is requested to establish bioequivalence between early clinical trial products and to-be-marketed products.

[063] For the blinded phase of the clinical Phase 2/3 trial, CT-ORZY-NPC-002, a capsule formulation with excess amount of excipient material for the lower capsule strengths was required in order to ensure blinding. The capsule formulation was then modified between the blinded and the open label (OL) phase of the CT-ORZY-NPC-002 trial in order to optimize it for the patients by reducing the capsule fill weight and

the amount of excipients to be taken with each capsule. Furthermore, the gelatin capsule shell was replaced with a shell of hydroxypropyl methyl cellulose (HPMC).

[064] Dissolution study of P741 arimoclomol citrate capsules at 3 different pH conditions in support of biowaiver.

[065] Dissolution testing were carried out in an Apparatus 2 at 75 rpm using 900 mL of the following dissolution media:

[066] - (1) Hydrochloric acid medium, pH 1.2;

[067] - (2) Acetate buffer solution, pH 4.5;

[068] - (3) Phosphate buffer solution, pH 6.8.

[069] Twelve dosage units for each strength of the test and reference drug product were evaluated in two separate sequences of 6 capsules each. Samples were collected at the time-points 5, 10, 15, 20, 30, 45 and 60 minutes to characterize the full dissolution profile of the drug product.

[070] - Batch 8211X (124 mg validation batch) – test product formula

[071] - Batch 8602X (93 mg validation batch) – test product formula

[072] - Batch 8106X (62 mg validation batch) – test product formula

[073] - Batch 8502X (47 mg validation batch) – test product formula

[074] - Batch 8404X (31 mg validation batch) – test product formula

[075] - Batch 16E03C (31 mg CTM batch) – reference product formula

[076] - Batch 16F07C (62 mg CTM batch) – reference product formula

Results

[077] For the reference product, both the 31 mg and the 62 mg dosage strength clearly show very rapid dissolution characteristics.

[078] For the test products, the 31 mg, 47 mg and 124 mg capsule strengths all dissolve in average 85% or more of the label claim of the drug within 15 minutes in all three dissolution media.

[079] For the test product at 62 mg dosage strength, in average 85% or more of the label claim of the drug dissolves within 15 minutes at pH 1.2 and 4.5. However, at pH 6.8, in average 84% of the label claim is dissolved at 15 minutes.

[080] Similarly, for the 93 mg dosage strength, where in average 85% or more of the label claim of the drug is dissolved within 15 minutes at pH 4.5 and 6.8, but at pH 1.2, in average 84% of the label claim is dissolved at 15 minutes.

[081] An analytical investigation was performed on the results for the test product batches of 62 mg and 93 mg dosage strengths that failed to meet the criterion of $\geq 85\%$ dissolved within 15 minutes at pH 6.8 and 1.2, respectively. Although no definitive methodological or analytical root cause could be established, it was found that these two tests showed the highest variability at 15 minutes in the whole study, RSD was 25.2 and 23.4% respectively. A Student's t-test showed a significant difference between the mean values obtained for sequence 1, i.e. vessel 1-6, and sequence 2, i.e. vessel 7-12 (FIG. 2).

[082] Individual differences in shell rupture and hydration of the capsule content leading to variability of dissolution between sequence 1 and 2 at early time points are considered the main contributors to the deviating results.

[083] As the dissolution results in the pivotal stability study is obtained at the same pH 1.2 that showed a mean of 84% dissolved of the label claim at 15 minutes, the result for the 93 mg dosage strength in this study can be compared to the data of the pivotal stability study. The mean result in the stability study at 15 minutes is $\geq 90\%$ at all 8 test points, indicating that the results obtained in this in vitro dissolution study are not representative of the test product. Corresponding stability data are not available for comparison of the 62 mg dosage strength at pH 6.8.

[084] Metabolism of arimoclomol was investigated in the human AME trial which included metabolite profiling of plasma, urine and feces (Trial AALS-002) and the 3 most abundant metabolites (M2, M5 and M105) were quantified in plasma and urine as part of the clinical trial (Trial OR-ARI-MET-01). In addition, several in vitro studies were conducted to identify the structure of the metabolites and the enzymes involved

in the metabolism of arimoclomol (please see the non-clinical part for further information).

[085] In both clinical trials arimoclomol was the primary component in both plasma and urine. In AALS-002, arimoclomol accounted for 43% of the total amount of radioactivity circulating in plasma and approximately 42% of the dose was excreted as intact arimoclomol in the urine, which is in agreement with results from OR-ARI-MET-01 where 43% of the dose was excreted as arimoclomol in urine.

[086] In vivo and in vitro studies together show that arimoclomol is metabolized by several routes and that the primary routes are by glutathionation, O-glucuronidation and NO-cleavage. The most abundant metabolites circulating in human plasma are the cysteine-conjugate (M2), the glucuronide (M5) and the cleavage product M105, which are also the most abundant metabolites in urine.

[087] All in vitro and vivo metabolism studies formed indicate that metabolism of arimoclomol is similar between humans and nonclinical species. Results from metabolite profiling in plasma obtained from animals and humans document that all human circulating metabolites were present in higher amounts in the nonclinical species.

Pharmacokinetics of metabolites

[088] The PK of arimoclomol and its metabolites was investigated in trial OR-ARI-MET-01 in six healthy young men aged ≥ 18 and ≤ 45 years. All subjects received 248 mg arimoclomol orally (capsules) t.i.d. (744 mg/day) on Day 1 to Day 5 and a single morning dose on Day 6. Plasma and serum samples were collected for up to 8 hours post-dose following the morning dose on Day 1, and plasma samples were collected pre-morning dose on Day 2, Day 3, Day 4, Day 5, and Day 6 and up to 168 hours post-dose following the last dose on Day 6. Urine was collected quantitatively up to 24 hours post-morning dose on Day 1, 2, and 6. The plasma exposure of arimoclomol and its metabolites M2, M5, and M105, following single- and multiple dosing, is illustrated in FIG. 3 and the pharmacokinetic parameters are summarized in FIG. 4, below.

[089] In addition, PK of arimoclomol and the metabolites M2 and M105 were investigated in a dedicated TQT trial (OR-ARI-TQT-01), including a total of 34 healthy male subjects. Metabolite M5 was not investigated in the trial, as it is an O-glucuronide and not of toxicological concern (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) 2012). The trial was completed in December 2020 and was submitted to EMA together with the responses to the D120. The PK profiles of arimoclomol citrate, M2 and M105 were captured after single and multiple doses of arimoclomol. The maximum observed plasma concentration was 6900 ng/mL for arimoclomol citrate, 2270 ng/mL for M2 and 833 ng/mL for M105. After dosing, arimoclomol was rapidly absorbed with a median Tmax of 1 hour for both the therapeutic and supratherapeutic arimoclomol dose on Day 1 and Day 3. The mean arimoclomol citrate exposure over the dose interval of 8 hours (AUC₀₋₈) increased from 5610 h*ng/mL after the therapeutic 124 (200) mg dose, to 18400 h*ng/mL after the supratherapeutic 372 (600) mg dose, both on Day 3. Therefore, a three-fold increase in dose level resulted in an at least 3 times higher mean exposure of arimoclomol citrate.

[090] FIG. 5-8 show the mean terminal half-life (t_{1/2}) of arimoclomol citrate in plasma on Day 3 was similar for the therapeutic and the supratherapeutic dose of arimoclomol (4.43 (11.6%) and 4.19 (9.7 %) hours, respectively). The metabolite M2 showed a slightly longer t_{1/2} (5.63 (10.4%) for the therapeutic dose and 5.40 (10.0%) for the supratherapeutic dose, as observed on Day 3) than arimoclomol citrate. As expected, the t_{1/2} for M105 could not be calculated as the terminal elimination phase for M105 plasma profile was not reached on Day 1 or Day 3 for neither the therapeutic nor the supratherapeutic arimoclomol dose. While the Day 1 plasma profiles showed rising M105 during the first dose interval of 8 hours, the Day 3 M105 profiles after t.i.d. dosing of both the therapeutic and supratherapeutic doses of arimoclomol show that M105 metabolite reached a steady state.

Dose proportionality

Arimoclomol is considered dose proportional within the dose range 62 to 372 mg t.i.d. (186 to 1116 mg/day). To investigate the dose proportionality of arimoclomol following

multiple doses, C_{max} and AUC₀₋₈ from all multiple-dose trials in healthy subjects were pooled as shown in FIG. 9.

[091] The population modelling did also confirm that pharmacokinetic of arimoclomol is linear within the dose range of 16 to 496 mg.

Time dependency

The CL/F was similar following single and multiple t.i.d. doses of arimoclomol (34 to 61 L/h; Table 3-3). From the population pharmacokinetics (popPK) analysis, no apparent time-dependency or non-linearity was observed as shown in FIG. 10.

[092] The pharmacokinetics of arimoclomol were demonstrated to be linear with increasing dose rates, and stable over the time course of treatment.

[093] Arimoclomol exhibit dose-proportional pharmacokinetics with an oral bioavailability of at least 42%. The absolute bioavailability of arimoclomol in humans was not investigated. In rats the absolute bioavailability of arimoclomol following oral administration was 84% and 75 % in dogs relative to arimoclomol i.v. administration (based on AUC_{0-inf}).

[094] Peak plasma concentration is reached within 0.25 to 3.0 hours (t_{max}). Food does not seem to have a relevant effect on pharmacokinetics. The effect of a high fat meal on the pharmacokinetics of 62 mg arimoclomol was determined in Trial AALS-004 and AALS-011. The 90% CI for the AUC_{0-t} and AUC_{0-inf}, and C_{max} ratios were within the limits of 80% to 125% in both studies. The median t_{max} was increased twofold in the fed versus the fasted state (3.0 versus 1.5 hours). However, since MIPLYFFA© is considered for long term use, the difference in t_{max} is, not deemed clinically relevant.

[095] The accumulation index for arimoclomol (based on AUC₀₋₈) was estimated to be 1.3 to 1.4 following multiple doses of 62 to 372 mg t.i.d (186 to 1116 mg/day). This is consistent with a mean half-life for arimoclomol of 3.0 to 4.4 hours and t.i.d. administration. No time dependency has been observed for the other pharmacokinetic parameters of arimoclomol.

PK in target population

FIG. 11 shows the summary statistics of arimoclomol exposure ($AUC_{0-8h,ss}$, $C_{min,ss}$ and $C_{max,ss}$) in CT-ORZY-NPC-002 for all patients and stratified by each of the 5 five weight bands.

[096] Furthermore, PK in target population was characterised using the popPK model, where the influence of age on absorption rate was observed, i.e., the absorption rate appears to increase with increasing age. In the D120 responses the applicant has provided a broader discussion to justify exclusion of age as a critical covariate. The method used for simulations is generally well described and considered suitable. It could be agreed that simulated results demonstrate minimal impact on C_{max} and AUC among different age groups, and, thus, it is agreed that the impact is negligible.

PK in special populationsImpaired renal function

[097] With the D180 responses the Applicant has submitted the final clinical trial report for the renal impairment trial OR-ARI-REN-01. For the results, please refer to the clinical safety part, section 3.3.9.11. "Additional data provided in D180 responses".

Impaired hepatic function

FIG. 12 shows the effect of hepatic impairment on the pharmacokinetics of arimoclomol following a single dose of 248 mg arimoclomol was investigated in an open-label, parallel-group, single-dose trial (OR-ARI-HEP-0) in twenty-four male and female subjects with mild and moderate hepatic impairment.

[098] The potential impact of various intrinsic factors, including age, gender, race and bodyweight have been examined by the use of population PK analyses as shown in FIG. 13-14.

[0099] Arimoclomol C_{maxss} is 19% lower and $AUC_{(0-8)ss}$ 15% lower in subjects with body weight above the median of 78.2 kg vs. subjects with a body weight equal to or below 78.2 kg. The weight range in the clinical studies is wide (11.7-114.2).

[0100] Not wanting to be bound by any particular theory, it is believed that Arimoclomol is an orally available small molecule that crosses the blood brain barrier (BBB). It amplifies and sustains the cellular production of HSPs, in particular HSP70 (Heat Shock Protein 70), through prolonged activation of HSF1 and induction of the HSR. HSP70 and other HSPs are critical to correct folding and processing of the integral lysosomal membrane protein NPC1, including the specific I1061T misfolding mutation, which is the most common form of mutated NPC1 in patients suffering from NPC. The HSR is linked directly to lysosomal integrity through HSP70 mediated stabilisation of lysosomal membranes and protection from cell death.

[0101] Thus, by amplifying the HSR, arimoclomol targets both protein misfolding and lysosomal dysfunction through a natural cellular defence mechanism. Arimoclomol therefore has a novel mechanism of action targeting the fundamentals of NPC aetiology: NPC protein misfolding and lysosomal dysfunction.

[0102] Primary pharmacology proof-of-concept was based on non-clinical studies with human biomaterials. Briefly, studies in NPC patient-derived fibroblasts and in $-/-$ NPC mice, which is the most used animal model for NPC, have been conducted. The dose dependant (50, 100, 200, 400 μ M) increase in NCP1 protein was observed in all eight tested NPC patient fibroblast cell lines carrying different mutations which were also found in phase 2/3 clinical trials, including I1061T, which is the most abundant missense mutation in NPC. In vivo studies in $-/-$ NPC mice demonstrated that brain HSF1 and HSP70 were upregulated in response to arimoclomol treatment.

[0103] PD markers were assessed as exploratory endpoints in the clinical study the CT-ORZY-NPC-002, the design of which is described in Clinical efficacy section. Chosen PD endpoints which are described in detail below, are considered relevant as they are important markers for NPC.

[0104] Three key biomarkers were evaluated: HSP70, un-esterified cholesterol, and cholestane-triol. Additional biomarkers evaluated were glycosphingolipids (GM3)

and nLc4. A significant influence of arimoclomol exposure was identified for the change in GM3 levels in PBMC (based on $AUC_{0-8,ss}$ and $C_{max,ss}$), where a higher exposure was associated with a decrease in GM3. No influence of arimoclomol exposure was identified for any of the other biomarkers analysed.

[0105] The mean HSP70 increase was higher in patients treated with arimoclomol compared to placebo during the 12 months treatment as measured in PBMCs; a mean increase in un-esterified cholesterol level in PBMCs was observed in both placebo and arimoclomol treated patients over 12 months. However, the mean increase, and hence accumulation, of un-esterified cholesterol was considerably lower in the arimoclomol group compared to the placebo group. Cholestane-triol levels in serum declined more in the arimoclomol treated patients compared to the placebo treated patients at 12 months.

[0106] Arimoclomol is metabolised by several routes and the three dominant pathways are glutathionation, O-glucuronidation and NO-cleavage. The most abundant metabolites circulating in plasma are the cysteine-conjugate of arimoclomol (M2) formed following hydrolysis of the glutathione-conjugate, the arimoclomol O-glucuronide (M5) and the cleavage product M105. Based on the in vitro pharmacology studies (induction of HSP70 mRNA in HeLa cells following heat shock and induction of NPC1 protein in human fibroblast cells) and their plasma exposures, none of the abundant metabolites M2, M5, or M105 is expected to contribute to the observed pharmacological effects of arimoclomol. Pharmacokinetic parameters of the most abundant metabolites M2, M5, and M105 have been investigated in 6 healthy volunteers following quantification of the metabolites in plasma and urine (OR-ARI-MET-01). Additionally, PK of arimoclomol and the metabolites M2 and M105 were investigated in a TQT trial (OR-ARI-TQT-01) in 34 healthy male subjects. The trial was completed in December 2020 and was submitted to EMA together with the responses to the D120 LoQ. Metabolite M5 was not investigated in the trial as it is an O-glucuronide and not of toxicological concern (ICH 2012). The results of the TQT trial constituted a negative TQT study according to the ICH E14 guidance. Furthermore, arimoclomol did not impact heart rate or cardiac conduction in the subjects in the trial and was well tolerated by the subjects at both the therapeutic (372 mg/day) and the

supratherapeutic (1116 mg/day) doses. When compared to the hepatic trial (OR-ARI-HEP-01), where subjects received a single dose of 248 mg arimoclomol, both the therapeutic and supratherapeutic doses were higher and the subjects were exposed to multiple doses.

[0107] The PK profiles of arimoclomol, M2 and M105 were captured after single and multiple doses of arimoclomol. The maximum observed plasma concentration was 6900 ng/mL for arimoclomol citrate, 2270 ng/mL for M2 and 833 ng/mL for M105. The mean arimoclomol citrate exposure over the dose interval of 8 hours (AUC₀₋₈) increased from 5610 h*ng/mL after the therapeutic 124 (200) mg dose, to 18400 h*ng/mL after the supratherapeutic 372 (600) mg dose, both on Day 3. Therefore, a three-fold increase in dose level resulted in an at least 3 times higher mean exposure of arimoclomol citrate. The mean terminal half-life (t_{1/2}) of arimoclomol citrate in plasma on Day 3 was similar for the therapeutic and the supratherapeutic dose of arimoclomol (4.43 (11.6%) and 4.19 (9.7 %) hours, respectively). The metabolite M2 showed a slightly longer t_{1/2} (5.63 (10.4%) for the therapeutic dose and 5.40 (10.0%) for the supratherapeutic dose, as observed on Day 3 than arimoclomol citrate. The t_{1/2} for M105 could not be calculated as the terminal elimination phase for M105 plasma profile was not reached on Day 1 or Day 3 for neither the therapeutic nor the supratherapeutic arimoclomol dose. While the Day 1 plasma profiles showed rising M105 during the first dose interval of 8 hours, the Day 3 M105 profiles after t.i.d. dosing of both the therapeutic and supratherapeutic doses of arimoclomol show that M105 metabolite reached a steady state.

[0108] In conclusion the TQT trial including a total of 34 healthy male subjects showed no safety concerns after multiple doses of arimoclomol up to 1116 mg/day and where the exposure to both metabolites (M2 and M105) reached a steady state.

[0109] Consequently, based on the results from the TQT trial no potential safety issue could be seen related to the metabolites and thus a dose reduction in patients with hepatic impairment may not be warranted.

[0110] The pharmacokinetic analysis suggested that age did not have a significant effect on the pharmacokinetics of arimoclomol in adults. However, the popPK model

has estimated K_a value around 0.338 h with CV= 48.5% and age was suggested as important factor for absorption. Provided simulations by applicant demonstrate that K_a has minimal impact on C_{max} and AUC among different age groups, and thus it is agreed that expected impact is negligible.

[0111] Sex and body weight (BW) were found to be significant covariates affecting the exposure of arimoclomol in adults. This effect might be related to the fixed dosing regimen in adults, with increased clearance with increasing body weight, and with women generally having a lower body weight than men. In the pivotal Phase 2/3 CT-ORZY-NPC-002 trial, subjects with body weight between 8 and 55 kg were dosed per body weight in pre-defined weight bands. Subjects above 55 kg received a fixed dose level of 124 mg t.i.d. arimoclomol. The observed effects of sex (AUC₀₋₈: 24%) and body weight (AUC₀₋₈: 15%, body weight below and above 78 kg) in adults are modest and not considered to be clinically relevant. Consequently, no dose adjustment of arimoclomol based on sex or age is necessary. The same fixed dosing regimen can be administered to all patients weighing > 55 kg.

[0112] Three dose forms were used in the Phase 2/3 trial CT-ORZY-NPC-002 (capsule, capsule emptied and dosed with food or drink, capsule emptied and dosed using gastric tube) to support administration in a population comprising paediatric patients and patients with swallowing difficulties. Thereof it was investigated whether these different dose forms could have an influence on the absorption rate (K_a). According to the applicant the analysis of the POP PK revealed that any influence of dose form was small and of no clinical relevance.

[0113] During the clinical development of arimoclomol for NPC, the drug product formulation has been modified with respect to the quantitative composition of the excipients. For the blinded phase of the clinical Phase 2/3 trial, CT-ORZY-NPC-002, a capsule formulation with excess amount of excipient material for the lower capsule strengths was required in order to ensure blinding. The capsule formulation was then modified between the blinded and the open label (OL) phase of the CT-ORZY-NPC-002 trial in order to optimise it for the patients by reducing the capsule fill weight and

the amount of excipients to be taken with each capsule. Furthermore, the gelatine capsule shell was replaced with a shell of hydroxypropyl methyl cellulose (HPMC).

[0114] To further ease compliance and avoid the ingestion of multiple capsules three times a day, a specific capsule strength for each recommended dose has since then been developed for the product covering each of the 5 weight bands. Consequently, the quantitative composition of the excipients was modified slightly for some of the strengths between the OL phase of the CT-ORZY-NPC-002 trial and the to-be-marketed product. In order to justify the use of the different drug product formulations used during the clinical development of arimoclomol for NPC and the to-be-marketed formulation, a biowaiver for bioequivalence studies is requested based on the BCS (Biopharmaceutics Classification System) approach. Generally, applying for a BCS-based biowaiver is restricted to drug products where the drug substance(s) exhibit high solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III) and known not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

[0115] The BCS prerequisite regarding high solubility has been demonstrated for Arimoclomol citrate under conditions as requested in the respective Guidelines (BE Guideline ICH9). Regarding permeability the applicant was asked to provide further data in order to clarify the BCS class for arimoclomol (BCS Class I or III). In its response the applicant provided data of a recently completed in vitro permeability study, using a validated Caco-2 test system and bioanalytical LC-MS method. Permeability was compared to the high and moderate permeability model drugs, minoxidil and atenolol, respectively. In this study, the in vitro cell line permeability for arimoclomol was similar to the highly permeable model drug minoxidil. Furthermore, the applicant was requested to provide information on possible excretion of arimoclomol or its metabolites in faeces by bile and whether unchanged drug contributes to the 12% recovered material in faeces. The applicant responded that stability studies have shown that arimoclomol is stable in gastric and intestinal fluids and as a consequence, the drug related material collected in faeces is expected to have its origins from arimoclomol that has previously been absorbed. Additionally, in

bile cannulated animals, the amount of drug related material excreted in bile was similar to the amount excreted in faeces in intact animals, which further indicates complete absorption of the oral dose of arimoclomol. Based on the data provided it was agreed that arimoclomol meets the requirements for high permeability which supports its designation as a BCS Class 1 drug.

[0116] To qualify for a BCS-based biowaiver for BCS Class I drug substances both the test product and reference product should display either very rapid ($\geq 85\%$ for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution characteristics, or rapid ($\geq 85\%$ for the mean percent dissolved in ≤ 30 minutes) and similar in vitro dissolution characteristics (i.e., based on f2 comparison).

[0117] For the reference product, both the 31 mg and the 62 mg dosage strength clearly showed very rapid dissolution characteristics.

[0118] For the test products, the 31 mg, 47 mg and 124 mg capsule strengths all dissolved in average 85% or more of the label claim of the drug within 15 minutes in all three dissolution media.

[0119] For the test product at 62 mg dosage strength, in average 85% or more of the label claim of the drug dissolves within 15 minutes at pH 1.2 and 4.5.

[0120] For the 93 mg dosage strength, where in average 85% or more of the label claim of the drug is dissolved within 15 minutes at pH 4.5 and 6.8.

[0121] In the blinded phase, arimoclomol or placebo capsules were administered orally three times a day (t.i.d.) for 12 months.

[0122] If IMP administration during the blinded phase coincided with the administration of other concomitant medication, the IMP was to be administered first.

[0123] If required, the IMP could be dissolved in 10 mL (i.e. 2 teaspoons) of liquid (water, apple juice, or milk) or in a tablespoon of soft foodstuff (yoghurt or apple sauce). In the dissolved or dispersed state, the IMP could also be administered via a gastric tube (as applicable).

[0124] A post-hoc analysis was performed excluding the 4 patients with a more aggressive progression pattern (FIG. 15).

[0125] In contrast to the small subgroup of 11 patients without miglustat treatment at baseline, the baseline demographics and disease severity were more balanced between the arimoclomol and placebo groups for the larger subgroup of 39 patients with use of miglustat at baseline (FIG. 16).

[0126] FIG 17 shows the analysis of change from baseline to Month 12 in the 5-domain and full-scale NPCCSS in subgroups based on age at first neurological symptom.

[0127] The 2 protocol-specified groups <3 months and 3 months to <2 years were collapsed into one group due to the low number of patients in this age span.

[0128] In one embodiment of the present technology is provided a method for diagnosing Niemann Pick disease, type C (NPC), in a human patient, the method comprising: performing a first assay test for at least one biomarker of arimoclomol to qualify as first level; administering a pharmaceutical composition comprising arimoclomol or a pharmaceutically acceptable salt thereof; performing a second assay for at least one metabolite of arimoclomol; performing a third assay test for the at least one biomarker of arimoclomol; and determining the difference between the first assay and the third assay. In another embodiment of the present technology is provided a method of treating a patient suspected to have NPC with a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof, wherein the patient has at least one biomarker selected from the group consisting of HSP70, unesterified cholesterol, cholestane-triol, glycosphingolipids (GM3) and nLc4, comprising administering a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof to the patient, wherein the administration of arimoclomol or pharmaceutically acceptable salt thereof to the patient results in one or more of the following: a) in a decrease in GM3; b) in an increase in HSP70; and/or c) in a decrease in cholestane-triol. For example the administration of arimoclomol to a patient who has NPC reduces accumulation of unesterified cholesterol in peripheral blood mononuclear cells. In another example, the administration of arimoclomol to a patient who has NPC reduces accumulation of serum cholestane-triol levels.

[0129] In another embodiment of the present technology is provided a method of treating Niemann Pick disease, type C (NPC), in a human patient in need thereof, wherein the patient has at least one biomarker selected from the group consisting of HSP70, unesterified cholesterol, cholestane-triol, glycosphingolipids (GM3) and nLc4, the method comprising administering a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof to the patient, wherein the amount of arimoclomol base in said composition or formulation is selected from the group consisting of 31 mg, 47mg, 62mg, 93mg or 124mg of arimoclomol. The NPC is either NPC-1 or NPC-2. The administration of arimoclomol or pharmaceutically acceptable salt thereof to the patient may result in one or more of the following: a) a decrease in GM3; b) in an increase in HSP70; and/or c) in a decrease in cholestane-triol. For example the administration of arimoclomol to a patient who has NPC reduces accumulation of unesterified cholesterol in peripheral blood mononuclear cells. In another example, the administration of arimoclomol to a patient who has NPC reduces accumulation of serum cholestane-triol levels.

[0130] In yet another embodiment of the present technology is provided a method of treating Niemann Pick disease, type C (NPC), in a human patient in need thereof, wherein the patient has at least one biomarker selected from the group consisting of HSP70, unesterified cholesterol, cholestane-triol, glycosphingolipids (GM3) and nLc4, the method comprising: first, providing a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof to the patient, wherein the pharmaceutical composition or formulation is presented or encapsulated in a capsule or other form, wherein further the amount of arimoclomol in said capsule (form) is selected from the group consisting of 31 mg, 47mg, 62mg, 93mg or 124mg of arimoclomol (base); second, opening the capsule and dispersing the pharmaceutical composition or formulation contents of the capsule into a liquid (e.g., suspension in water) or solid medium, wherein the liquid medium is selected from the group consisting of water or apple juice, and wherein the solid medium is selected from the group consisting of soft food (e.g., applesauce, gelatin, baby food, among others for use with neonatal, pediatric, and other patients requiring such soft mediums); and third administering the liquid or solid medium of step b) to the patient

within 24 hours from (after) the dispersion of the pharmaceutical composition or formulation of the capsule into the liquid or solid medium via a mode of administration, wherein the mode of administration is selected from the group consisting of oral (i.e. swallowing or drinking), gastric insertion or feeding tube.

[0131] In another embodiment of the present technology is provided a method of treating Niemann Pick disease, type C (NPC), in a human patient in need thereof, the method comprising the steps of: first, providing to the patient a sufficient amount of a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof, wherein the composition or formulation of arimoclomol is provided in a capsule or capsular dosage form, and the sufficient amount is selected from the group consisting of 31mg, 47mg, 62mg, 93 mg and 124 mg or arimoclomol (base form); second, opening the capsule or capsular dosage form and dispersing the pharmaceutical composition or formulation of arimoclomol or the pharmaceutically acceptable salt thereof in at least one liquid or at least one solid medium to form at least one dispersion; and finally third administering the dispersion to the patient within a twenty-four period of time after the pharmaceutical composition or formulation, or the pharmaceutically acceptable salt thereof, is dispersed within the at least one liquid or solid medium. In other words, the dispersion is administered in to the patient within 24 hours of the formation of the dispersion. In these embodiments, the liquid medium may be one or at least one member selected from the group consisting of water and apple juice or a combination thereof. Furthermore, the solid medium in these embodiments may be selected from the group consisting of at least one soft food, (e.g., applesauce, gelatin, baby food, among others for use with neonatal, pediatric, and other patients requiring such soft mediums).

[0132] In yet another embodiment of the present technology, the administration to the NPC patient of the pharmaceutical composition or formulation of arimoclomol, or pharmaceutical salt thereof, or of the dispersion of the pharmaceutical composition or formulation of arimoclomol, or pharmaceutical salt thereof into a liquid or solid medium, may be done orally, such as but not limited to insertion into the mouth and swallowing, via a nasogastric tube, via a gastric tube, or via a non-gastric feeding tube. In some embodiments of the present technology, the patient is over two years of age.

In alternative embodiments of the present technology, the patient is two years of age or less (such as an infant).

[0133] In some embodiments of the present technology, the pharmaceutically acceptable salt of arimoclomol is arimoclomol citrate. In other embodiments of the present technology, the Niemann Pick disease, type C (NPC) is either sub-type NPC1 (NPC1 or NPC-1) or sub-type NPC2 (NPC2 or NPC-2).

[0134] In yet another embodiment of the present technology is provided a monotherapy method of treating a patient with NPC with a pharmaceutical composition or formulation of arimoclomol, or a pharmaceutically acceptable salt thereof. For example, in some of these monotherapy methods, the patient is not suitable for treatment with another medicament, such as for example treatment with miglustat.

[0135] In an alternative embodiment of the present technology is provided a dual or combinatorial therapy method of treating a patient with NPC with a pharmaceutical composition or formulation of arimoclomol, or a pharmaceutically acceptable salt thereof, in addition to a sufficient amount of a pharmaceutical composition or formulation of miglustat. A sufficient amount of miglustat, or its pharmaceutical composition or formulation, may be a therapeutically effective amount.

[0136] In yet another embodiment of the present technology, the administration of the pharmaceutical composition or formulation of arimoclomol, or a pharmaceutically acceptable salt thereof to the patient in need thereof may result in the formation of at least one or more metabolites. The metabolites may be present in the composition or formulation prior to administration, or may form and be present in the dispersion during the dispersing step discussed herein, or may form after administration to the patient. The at least one or more metabolites are selected from the group consisting of M1, M2, M3, M4, M5, M7, M39, M104, M105 and M 107. In one example of the present technology the at least one metabolite is one or more of the following: M2, M5, or M105.

[0137] In another embodiment of the present technology, the dispersing step of the pharmaceutical composition or formulation of the arimoclomol, or the

pharmaceutically acceptable salt thereof, into the at least one liquid medium results in at least 80% of the pharmaceutical composition or formulation of the arimoclomol, or the pharmaceutically acceptable salt thereof, being suspended or dissolved in the at least one liquid medium. For example, at least 80% of the pharmaceutical composition or formulation of the arimoclomol, or the pharmaceutically acceptable salt thereof, is dissolved in the liquid medium within 15 minutes following the dispersion/dispersing step. In one embodiment of this present technology, at least 80% of the pharmaceutical composition or formulation of the arimoclomol citrate is dissolved in the liquid medium within 15 minutes of the dispersion step (i.e. dispersion of the arimoclomol citrate into said liquid medium). The at least one liquid medium has a pH range of about 1.2 to about 6.8. In one embodiment, the liquid medium has a pH range of about 1.2 to about 4.5.

Claims

1. A method of treating Niemann Pick disease, type C (NPC), in a human patient in need thereof, the method comprising the steps of:
 - providing to the patient a sufficient amount of a pharmaceutical composition or formulation of arimoclomol or a pharmaceutically acceptable salt thereof;
 - wherein the composition or formulation of arimoclomol is provided in a capsular dosage form; and
 - wherein the sufficient amount of the pharmaceutical composition or formulation of arimoclomol, or the pharmaceutically acceptable salt thereof, is selected from the group consisting of 31 mg, 47mg, 62mg, 93mg, and 124mg of arimoclomol (base form);
 - opening the capsular dosage form and dispersing the pharmaceutical composition or formulation of arimoclomol or the pharmaceutically acceptable salt thereof in at least one liquid or at least one solid medium to form at least one dispersion; wherein the liquid medium is at least one member selected from the group consisting of water and apple juice;
 - wherein the solid medium is at least one soft food; and
 - administering the dispersion to the patient within a twenty-four period of time after the pharmaceutical composition or formulation, or the pharmaceutically acceptable salt thereof, is dispersed or suspended within the at least one liquid or solid medium.
2. The method of claim 1, wherein the administration step is performed orally, via a nasogastric tube, via a gastric tube, or via a non-gastric feeding tube.
3. The method of claim 1, wherein the pharmaceutically acceptable salt of arimoclomol is arimoclomol citrate.
4. The method of any of claims 1-3, wherein the patient is under the age of two years.

5. The method of claim 1, wherein the soft food is applesauce.
6. The method of claim 1, the liquid medium is apple juice.
7. The method according to either claims 1 or 2, wherein the liquid medium is water; and
wherein the dispersion is administered to the patient via at least one gastric or non-gastric feeding tube.
8. The method according to any one of claims 1-7, wherein the Niemann Pick disease, type C is either sub-type NPC1 or sub-type NPC2.
9. The method according to any of claim 1-8, further comprising the step of administering to the patient a sufficient amount of miglustat to the patient.
10. The method according to any one of claims 1-8, wherein the method of treatment is a monotherapy with arimoclomol, or pharmaceutically acceptable salt thereof.
11. The method of treatment according to any one of claims 1-10, where in the pharmaceutical composition or formulation of arimoclomol, or a pharmaceutically acceptable salt thereof, is metabolized by the patient into at least one metabolite of arimoclomol.
12. The method of treatment of claim 11, wherein the at least one metabolite is a member selected from the group consisting of M1, M2, M3, M4, M5, M7, M39, M104, M105 and M 107.
13. The method of claim 12, wherein the metabolite is M2, M5, or M105.

14. The method of claim 1, wherein at least 80% of the pharmaceutical composition or formulation of the arimoclomol, or the pharmaceutically acceptable salt thereof, is dissolved in the liquid medium within 15 minutes following the dispersion step.
15. The method of claim 3, wherein at least 80% the arimoclomol citrate is dissolved in the liquid medium within 15 minutes following the dispersion step.
16. The method according to either claims 14 or 15, wherein the liquid medium has a pH range of about 1.2 to about 6.8.
17. The method of claim 16, wherein the liquid medium has a pH range of about 1.2 to about 4.5.