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ADISINSIGHT REPORT

Arimoclomol: First Approval

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Abstract
Arimoclomol (MIPLYFFA™), an oral small molecule that crosses the blood brain barrier and is thought to upregulate CLEAR (Coordinated Lysosomal Expression and Regulation) network genes and improve lysosomal function, is being developed by Zevra Therapeutics Inc., for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC). In September 2024, arimoclomol was approved for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients 2 years of age and older in the USA. This article summarizes the milestones in the development of arimoclomol leading to this first approval for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients aged ≥ 2 years.

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Arimoclomol (MIPLYFFA™): Key Points

An oral small molecule that crosses the blood brain barrier and is thought to upregulate CLEAR network genes and improve lysosomal function is being developed by Zevra Therapeutics for the treatment of neurological manifestations of NPC

Received its first approval on 20 September 2024 in the USA

Approved for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients 2 years of age and older

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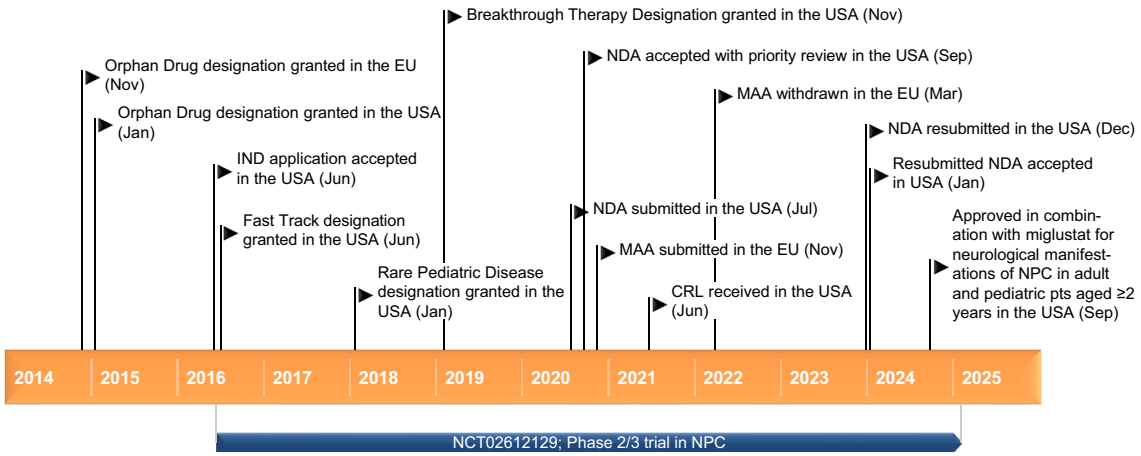
1 Introduction

Niemann-Pick disease type C (NPC) is a rare, inherited, progressive, neurodegenerative lysosomal storage disorder caused by mutations in either the *NPC intracellular cholesterol transporter 1* (*NPC1*; 95% of cases) or *NPC2* gene. Disease-modifying therapies for NPC are limited and there is an urgent unmet need for new therapeutic options [1, 2]. The primary defect in NPC relates to proteins that ensure the homeostasis of cholesterol in cells. NPC is characterized by a toxic accumulation of lipid species, which is caused by absent or dysfunctional NPC proteins leading to impaired lysosomal function and ultimately cell death [1–3]. Upregulation of CLEAR (Coordinated Lysosomal Expression And Regulation) network genes, including *NPC1* and *NPC2*, in affected cells could help improve lysosomal biology to reduce the toxic accumulation of lipid species [4].

Arimoclomol (MIPLYFFA™), an oral small molecule that crosses the blood brain barrier and is thought to facilitate enhanced expression of CLEAR genes and improve lysosomal function (although the clinical significance of these findings is not fully understood), is being developed by Zevra Therapeutics Inc., for the treatment of neurological manifestations of NPC [5–7]. In September 2024, arimoclomol was approved for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients 2 years of age and older in the USA [5, 6, 8]. Arimoclomol can be administered with or without food [5].



Key milestones in the development of arimoclomol in the treatment of Niemann-Pick disease type C. *CRL* complete response letter, *IND* investigational new drug, *MAA* marketing authorization application, *NDA* new drug application, *NPC* Niemann-Pick disease type C

The recommended oral dosage of arimoclomol, in combination with miglustat, is weight based. In patients with an actual body weight of 8–15 kg, the dosage is 47 mg 3 times a day; in those weighing > 15 kg to 30 kg, the dosage is 62 mg 3 times a day; in those weighing > 30 kg to 55 kg, the dosage is 93 mg 3 times a day; and in those weighing > 55 kg, the dosage is 124 mg 3 times a day. In patients with mild renal impairment (eGFR ≥ 50 mL/min) the recommended dosage regimen is the same as that in patients with normal renal function. In patients with moderate to severe renal impairment (eGFR 15 mL/min to < 50 mL/min), the recommended dosing frequency of arimoclomol is reduced to 2 times a day [5]. Hypersensitivity reactions such as urticaria and angioedema were reported in the clinical trial in patients with NPC. These reactions occurred within the first 2 months of treatment. If a mild or moderate hypersensitivity reaction occurs, arimoclomol should be stopped, the reaction treated promptly and the patient monitored until signs and symptoms resolve. If a severe hypersensitivity reaction occurs, discontinue treatment with arimoclomol [5]. In clinical trials, arimoclomol administration was associated with an increase in serum creatinine (mean 10–20% from baseline). The increases occurred mainly within the first month of treatment. Glomerular function and renal hemodynamics were not affected and increases in serum creatinine reversed on discontinuation of arimoclomol. The increase in serum creatinine may be due to inhibition of renal tubular secretion transporters and alternative measures that are not based on serum creatinine should be used to assess renal function during arimoclomol treatment [5].

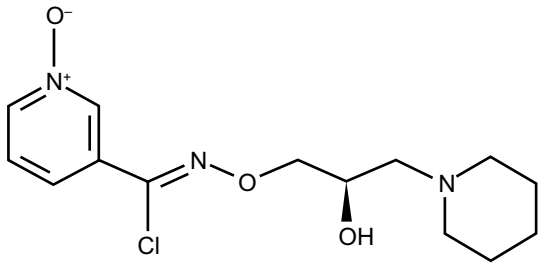
1.1 Company Agreements

In June 2023, LadRx corporation (formerly CytRx corporation [9]) completed a non-dilutive financing transaction (that included transfer of the royalty and milestone rights associated with arimoclomol) with XOMA corporation [10, 11]. In May 2022, Zevra Therapeutics (formerly KemPharm Denmark A/S [12]) announced a definitive agreement with Orphazyme A/S to acquire Orphazyme's assets, including arimoclomol [13, 14]. In May 2011, LadRx sold worldwide rights to its molecular chaperone assets, including arimoclomol, to Orphazyme in exchange for milestone payments and royalties [15].

2 Scientific Summary

2.1 Pharmacodynamics

Treatment of healthy human and NPC patient-derived fibroblasts with arimoclomol in vitro induced general activation of the CLEAR network. Arimoclomol activation of the transcription factors EB (TFEB) and E3 (TFE3) within the CLEAR pathway increased transcription of several lysosome-related genes, including *NPC1* and *NPC2*. *NPC1* transcriptional upregulation correlated with a significant increase of correctly processed NPC1 protein [4, 7].



Arimoclomol chemical structure

Treatment of *NPC1* patient fibroblasts with arimoclomol in vitro significantly reduced lysosomal storage and the accumulation of unesterified cholesterol [7, 16]. In the *Npc1*$^{-/-}$ (*Npc1*^{nih}) mouse model of NPC, treatment with arimoclomol reactivated heat shock factor 1(HSF1) and completely restored heat shock protein 70 (HSP70) levels in the brain, improved ataxia, respiration rate and eyelid closure, and increased survival [16]. In the same mouse model of NPC, improved myelination and an increase in the number of mature oligodendrocytes and the ratio of active-to-inactive forms of phosphorylated Fyn kinase in the cerebellum of mice was evident with bimoclomol (an arimoclomol analogue). Bimoclomol preserved cerebellar weight and increased the numbers of immature oligodendrocytes within the cortex [17].

In a phase 2/3 trial (NCT02612129) in patients with NPC, treatment with arimoclomol for 12 months was associated with a significant ($p = 0.001$) increase from baseline in HSP70 levels in peripheral blood mononuclear cells (PBMCs) [18]. Plasma Lyso-SM-509 levels were significantly ($p = 0.043$) reduced relative to placebo at month 12 [18], and patients treated with arimoclomol for 36 months showed reductions in serum cholestane-triol levels and unesterified cholesterol accumulation in PMBCs [19].

Administration of arimoclomol 124 mg and 372 mg 3 times daily in healthy adult subjects in a thorough QTc study did not prolong the QTc interval to a clinically relevant extent [5].

2.2 Pharmacokinetics

The pharmacokinetic profile of oral arimoclomol was linear and dose proportional after oral administration of arimoclomol 62–372 mg 3 times daily in healthy subjects [5]. The absolute bioavailability of oral arimoclomol has not been determined. Median t_{max} was ≈0.5 h. At steady state in heathy adult subjects, mean V_Z/F was 211 L and a dose-dependent increase in arimoclomol concentrations in cerebrospinal fluid was observed. Arimoclomol is ≈10% plasma protein bound [5]. In pediatric patients with NPC, the estimated mean $C_{max,ss}$ is 523 ng/mL and estimated $C_{trough,ss}$ is 206 ng/mL after administration of the recommended dosing regimens [5]. Arimoclomol is predominantly metabolized through glutathionation, *O*-glucuronidation and NO-oxime cleavage. In healthy adult subjects, the arimoclomol $t_{1/2}$ was ≈ 4 h and mean CL/F_{ss} was 34 L/h. Arimoclomol is primarily excreted via the kidneys. In healthy male subjects, 77.5% of a single 100 mg dose of radiolabelled arimoclomol was recovered in urine (42% as the unchanged drug) and ≈12% was recovered in feces [5].

Compared with subjects with normal renal function (eGFR ≥ 90 mL/min), total exposure (AUC_f) to arimoclomol was increased ≈ 2-fold in subjects with moderate to severe renal impairment (eGFR 15–49 mL/min) [5]. Mild renal impairment (eGFR ≥ 50 mL/min) and mild or moderate hepatic impairment (Child-Pugh Score A or B) had no clinically relevant impact on arimoclomol pharmacokinetics; arimoclomol has not been studied in patients with an eGFR < 15 mL/min or with severe hepatic impairment (Child-Pugh Score C) [5].

In vitro studies indicate that arimoclomol is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, and is not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1 and MATE2-K transporters [5]. Arimoclomol is an inhibitor of OCT2 and may increase exposure of OCT2 substrates, including the endogenous substrate creatinine. If arimoclomol is used concomitantly with OCT2 substrates, monitor for adverse reactions and reduce the dosage of the OCT2 substrate. Arimoclomol is a substrate of MATE1 and MATE2-K transporters, although MATE1 and MATE2-K inhibitors are not expected to have a clinically relevant effect on arimoclomol exposure [5].

2.3 Therapeutic Trials

Treatment with arimoclomol slowed NPC disease progression in the 12-month, phase 2/3 randomized, double-blind, placebo-controlled trial in pediatric patients with NPC (NCT02612129) [18]. The mean change from baseline in the validated 5-domain Niemann-Pick type C Clinical Severity Scale (5NPCCSS) total score at month 12 in the full analysis set (FAS; $n = 50$) [primary endpoint] was significantly lower with arimoclomol ($n = 34$) than with placebo ($n = 16$) [0.76 vs 2.15; treatment difference –1.40 (95% CI –2.76 to –0.03); $p = 0.046$]. A significant between-group difference favouring arimoclomol was also seen in the subgroup of patients also receiving miglustat ($n = 26$ arimoclomol and 13 placebo recipients) [–0.06 vs 2.01; treatment difference –2.06 (95% CI–3.49 to –0.63); $p = 0.006$] [18]. The 5DNPCCSS evaluated 5 domains (swallow, fine motor skills, speech, ambulation and cognition) of the 17-domain NPCCSS [20]. A 1- to 2-point change in the 5DNPCCSS represents a clinically meaningful change or progression; any slowing of disease is considered meaningful [20]. At baseline, mean 5DNPCCSS total score was 12.1 in the arimoclomol arm and 9.4 in the placebo arm [18].

The rescored 4-domain version of the NPCCSS (RD4NPCCSS), which omitted the cognition domain and applied a more linear scoring algorithm to the swallow domain, was considered more appropriate for a 12-month clinical trial in patients with a wide age range [21]. Mean R4DNPCCSS total score at baseline was 8.9 in the arimoclomol plus

Features and properties of arimoclomol

Alternative names	Arimoclomol citrate; MIPLYFFA; BRX-345
Class	Anti-inflammatories, Antineoplastics, Antiparkinsonians, Chlorinated hydrocarbons, Hydroxylamines, Oxides, Piperidines, Pyridines, Small molecules
Mechanism of action	Unknown
Route of administration	Oral
Pharmacodynamics	Induced general activation of the CLEAR pathway, including TFEB and TFE3 Reduced lysosomal storage and the accumulation of unesterified cholesterol in vitro Restored brain HSP70 levels, improved ataxia, respiration rate and eyelid closure, and increased survival in a mouse model of NPC Increased HSP70 levels and reduced levels of plasma Lyso-SM-509 and serum cholestane-triol and unesterified cholesterol accumulation in patients with NPC
Pharmacokinetics	Estimated mean $C_{max,ss}$ 523 ng/mL; estimated $C_{trough,ss}$ 206 ng/mL; median t_{max} ≈0.5 h; mean V_Z/F 211 L; $t_{1/2}$ ≈ 4 h; mean CL/F_{ss} 34 L/h. Dose-dependent ↑in CSF concentrations
Adverse events	
Most frequent	URTI, diarrhea, ↓ weight, ↓ appetite , tremor, urticaria ± angioedema, headache, LRTI, seizure
ATC codes	
WHO ATC code	N07X-X17 (Arimoclomol)
EphMRA ATC code	A10X (Other Drugs Used in Diabetes); L1 (Antineoplastics); M5X (All Other Musculoskeletal Products); N4 (Anti-Parkinson Drugs); N7X (All other CNS drugs)
Chemical name	N-[(2R)-2-hydroxy-3-piperidin-1-ylpropoxy]-1-oxidopyridin-1-ium-3-carboximidoyl chloride;2-hydroxypropane-1,2,3-tricarboxylic acid

miglustat arm and 7.0 in the placebo plus miglustat arm [5]. Arimoclomol, in combination with miglustat ($n = 22$ evaluable), stabilized disease progression through 12 months' treatment, evidenced by a –0.2 point change from baseline in the R4DNPCCSS compared to a 1.9 point increase from baseline for patients treated with placebo with miglustat ($n = 12$ evaluable). The mean change from baseline in the R4DNPCCSS score at 3, 6 and 9 months in arimoclomol with miglustat recipients was –0.3, –0.1, and –0.3, respectively, compared with 0.4, 1.3 and 1.7 in placebo with miglustat recipients [5]. In the cohort of patients who continued arimoclomol in the 4-year, open-label extension (OLE) [$n = 26$], the mean change from baseline in the R4DNPCSS total score was 0.6 at entry into the OLE, 1.4 at year 1, 1.1 at year 2, 0.3 at year 3 and 0.8 at year 4. In placebo recipients who switched to arimoclomol in the OLE ($n = 15$), the mean change from baseline in R4DNPCSS was 1.9 at entry, 0.3 at year 1, < 0.3 at years 2 and 3 and 0.8 at year 4 [22].

In the 12-month phase 2/3 trial, patients aged 2–19 years were randomized to receive weight-adjusted oral doses of arimoclomol 31–124 mg three times daily or matching placebo. Of these patients, 26 arimoclomol recipients and 13 placebo recipients were receiving miglustat as part of routine clinical care and continued this treatment throughout the trial. The remaining 11 patients did not receive miglustat treatment [18]. In patients who received concomitant miglustat, mean age at baseline was 11.6 years [18].

In pediatric and adult patients with NPC ($n = 56$) who were treated with arimoclomol in the US expanded access program (EAP), the mean change from baseline in the 5DNPCCSS total score at years 1, 2 and 3 were—0.9, 0.3 and 0.1 in those receiving miglustat as part of routine clinical care ($n = 31$, 22 and 15, respectively) and 0.8, 1.0 and 1.0 in those who were not receiving miglustat ($n = 24$, 23 and 13, respectively). Corresponding mean changes from baseline in the 4DNPCCSS total score at years 1, 2 and 3 were—0.8, 0.1 and 0.1 in those receiving miglustat and 0.4, 0.9 and 1.2 in those who were not receiving miglustat. At baseline, median age was 20.5 years (range 2–41 years); 5DNPCCSS and 4DNPCCSS total scores were 11.0 and 8.1 in the miglustat use group and 11.7 and 8.5 in the no miglustat use group [23].

Key clinical trials of arimoclomol (Zevra Therapeutics Inc.)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Arimoclomol, placebo	Niemann-Pick disease type C	2/3	Completed	USA, Europe	NCT02612129; EudraCT2015-004438-93
Arimoclomol	Niemann-Pick disease type C	EAP	Completed	USA	NCT04316637

2.4 Adverse Events

The most common (incidence ≥ 8%) adverse reactions in the 12-month phase 2/3 trial (NCT02612129) in which a subgroup of pediatric and adolescent patients with NPC were treated with arimoclomol ($n = 26$) or placebo ($n = 13$) plus miglustat were upper respiratory tract infection (31% vs 15%), diarrhea (23% vs 23%), decreased weight (15% vs 0%), decreased appetite (12% vs 0%), tremor (12% vs 0%), urticaria with/without angioedema (12% vs 0%), headache (12% vs 8%), lower respiratory tract infection (12% vs 8%) and seizure (12% vs 8%) [5]. Three (6%) arimoclomol plus miglustat recipients withdrew from the trial because of adverse reactions [increased serum creatinine (one patient), and progressive urticaria and angioedema (two patients)]. Serious adverse reactions reported in arimoclomol plus miglustat recipients were hypersensitivity reactions including urticaria and angioedema [5]. Among 41 patients who entered the open-label extension of the phase 2/3 trial and were treated with arimoclomol for a further 48 months, the overall pattern and frequency of adverse reactions reported was comparable with that in the double-blind phase. The most frequent adverse reactions were diarrhea (24.4%) and upper respiratory tract infections (24.4%) [22].

The safety profile of arimoclomol in pediatric and adult patients with NPC ($n = 94$) who received treatment with arimoclomol ($n = 32$) or arimoclomol plus miglustat ($n = 62$) over more than 2 years in the EAP was consistent with that seen in the phase 2/3 clinical trial of arimoclomol in patients with NPC [24].

2.5 Ongoing Clinical Trials

The Phase 2/3 trial and open label extension have ended, however the paediatric sub-study in patients aged 6–24 months is ongoing (NCT02612129).

3 Current Status

Arimoclomol received its first approval on 20 September 2024 for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and paediatric patients aged ≥ 2 years in the USA [5, 6, 8]. Arimoclomol is being made available to patients with NPC in Europe under various EAP programs [25].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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