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# Real World Data Collection in Niemann-Pick Disease Type C – Data from Expanded Access Program with Arimoclomol

**Elizabeth M. Berry-Kravis[1], Daniel Gallo[2], Kristin Pagano[2], Ronan O'Reilly[2], Conan Donnelly[3]**

[1] Rush University Medical Center, Chicago, IL, USA, [2] Zevra Therapeutics, Orlando, FL, USA, [3] INPDR, Washington, Tyne & Weir NE37 2SQ, UK

52nd Annual Child Neurology Society Meeting, Vancouver, BC, Canada, October 4-7, 2023

## OBJECTIVE

- Niemann-Pick disease Type C (NPC) is a rare, progressive, neurodegenerative disease with no FDA-approved treatments and persisting unmet medical need.
- Arimoclomol is an investigational orally available small molecule for the treatment of NPC.
- Rare disease data are sparse and data collection opportunities limited.
- Randomized controlled trials remain the data collection gold standard, however, real-world data (RWD) can contribute additional and important insights as increasingly recognized by regulatory authorities.
- RWD collected in an ongoing protocol-driven Expanded Access Program (EAP) aim to expand the understanding of NPC, including in populations not previously studied in controlled clinical trials.
- Furthermore, data collected will be transferred (with consent) to the International Niemann-Pick Disease Registry (INPDR) to contribute to a single world-wide source of NPC RWD.

## METHODS AND RESULTS

### Design and setup

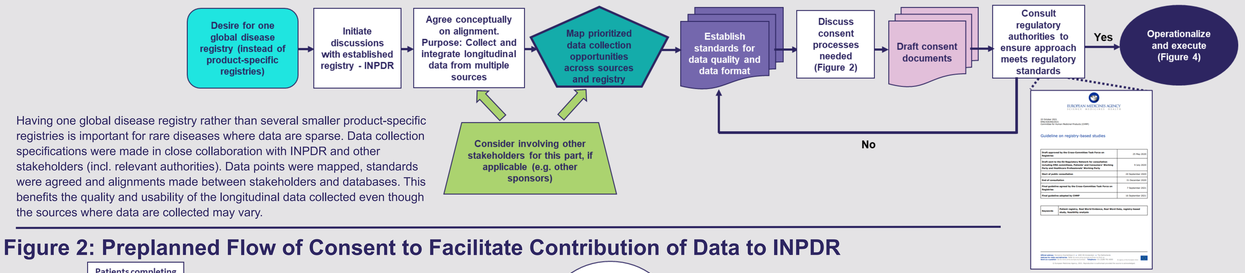
- For the data collection specifications of the arimoclomol EAP, we cooperated with INPDR - a disease-specific worldwide registry which aims to support diagnosis, improve clinical care and advance research in NPC (**Figure 1 and 2**).
- Through the EAP, early access to arimoclomol is provided for a group of NPC patients, neither eligible for nor able to participate in clinical trials (**Table 1**) and who, in the opinion and clinical judgement of the treating physician, may benefit from treatment with arimoclomol prior to its potential marketing authorization.
- The arimoclomol EAP was designed to provide expanded access to patients in 7 countries, with 44 sites globally.
- RWD are primarily collected in the US and the focus of this poster is therefore on the US arimoclomol EAP (clinicaltrials.gov ID: NCT04316637).
- The 15-site US arimoclomol EAP was designed to maximize data capture in this rare disease population, while decreasing burden of participation on patients, caregivers, and staff through inclusion of broad geographic site representation (**Figure 3**), telemedicine consultations, direct-to-patient shipment, and local laboratories for blood tests (**Figure 4**).

### Table 1: EAP Eligibility and Ineligibility Criteria

| Eligibility Criteria | Ineligibility Criteria |
|---|---|
| Confirmed NPC diagnosis and at least 1 neurological symptom | Severe liver insufficiency |
| Age ≥ 2 years | Renal insufficiency |
| Permanent US resident | Known or suspected allergy or intolerance to arimoclomol or its constituents |
| If taking miglustat (Zavesca®), the patient must have been on the target dose for the past 6 weeks | Pregnancy, planning to become pregnant (during the EAP) or currently breastfeeding |
| Sexually active females of child-bearing potential must agree to use highly effective contraception | Plans for treatment with other investigational drug during the EAP or in the 4 weeks prior to arimoclomol treatment start |
| Confirmed negative pregnancy test for sexually active females | The patient is either eligible and able to participate in or is currently participating in an active interventional clinical trial within the indication |
| Sexually active male patients with female partners of child-bearing potential agree to use a condom in addition to birth control used by their partners | The patient, in the opinion of the clinician, is unable to comply with the treatment or has a medical condition that would potentially increase the risk to the patient by participation |
| If history of seizures, the condition must be adequately controlled, i.e., seizure activity must be stable, and patient must be on stable dose and regimen of antiepileptic medication during 1 month prior to screening | The patient has a medical condition which hinders the clinician's assessment of arimoclomol safety and efficacy (e.g. certain epileptic conditions or severe cataplexy) |
| Written informed consent (patient or parent/guardian) | |
| For participants in CT-ORZY-NPC-002 clinical trial: The treating physician confirms a positive benefit risk assessment for the patient at end of trial. | |

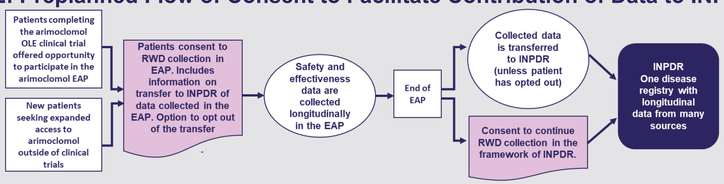
## METHODS AND RESULTS

### Figure 1: EAP Setup and Data Capture Specification in Collaboration and Alignment with Worldwide Registry - INPDR



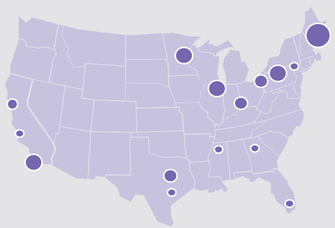

Having one global disease registry rather than several smaller product-specific registries is important for rare diseases where data are sparse. Data collection specifications were made in close collaboration with INPDR and other stakeholders (incl. relevant authorities). Data points were mapped, standards were agreed and alignments made between stakeholders and databases. This benefits the quality and usability of the longitudinal data collected even though the sources where data are collected may vary.

### Figure 2: Preplanned Flow of Consent to Facilitate Contribution of Data to INPDR

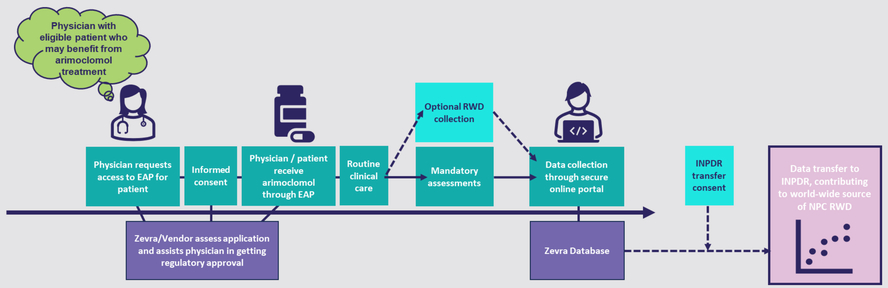



To facilitate collection of longitudinal data and contribution to INPDR beyond the EAP, the consent process for various steps was mapped ahead of EAP initiation.

### Figure 3: The EAP has Broad Geographic Representation in USA



### Figure 4: EAP Design with Minimized Burden for Patients, Caregivers and Staff




### Table 2: Mandatory (A) and Optional (B) Data Collection

| A Data Type | Data Element / Description |
|---|---|
| Enrollment | Country , Site , RWD Consent , Gender , Year of Birth |
| Demography | Race , Height , Weight |
| NPC diagnosis | DNA Testing for NPC1, NPC2 mutations and further genetic variants, Cytochemical and Oxysterol testing (if performed) |
| Treatment Initiation | Patient Age , Treatment Initiation Date, Initial Dose |
| Repeating Arimoclomol Treatment | Height , Weight , Dosing Strength Dates and adjustments |
| Laboratory data | Results Units and Ranges |
| Safety | Serious Adverse Events and non-serious AEs considered related to arimoclomol |

| B Data Type | Data Element / Description |
|---|---|
| Demography | Age of diagnosis , Ethnicity. |
| NPC Diagnosis | Age when Diagnostic Tests Performed , Name of Labs where tests are performed , Dates of Tests. |
| Physical Examination | Examination of the patient's general physical condition. |
| NPC Disease History | Age at First observed for Visceral Abnormalities , Neurological Development and Impairments and other relevant NPC diseases (If present) |
| Medical History | Details of any non-NPC related significant diseases |
| 5-domain NPCCSS | A disease-specific and validated measure of disease progression, consisting of the five clinically most relevant domains (cognition, speech, swallow, fine motor skills and ambulation) (**Table 3**). |
| Concomitant Medication | Specification of any medication taken by the patient during the last six weeks prior to enrollment. New and changed medications. |

## METHODS AND RESULTS

### Mandatory and Optional Data Collection

- Routine clinical care is maintained, with clinical assessments at baseline and months 1, 4, 7 and 12. Beyond this, data are collected at routine follow-up visits.
- Training is provided to ensure consistent and reliable scoring of the NPC Clinical Severity Scale (NPCCSS) (**Table 3**).
- Effectiveness and safety data are collected through a secure online portal.
- Limited mandatory assessments are required for participation in the EAP (**Table 2, A**) while some RWD collection is optional (**Table 2, B**).
- 98% percent of patients have consented to RWD collection in the US (data on file).
  - Of these, 96.3% contribute physician-reported 5-domain NPCCSS scores.
    - 60.9% currently contribute a minimum of 1 year 5-domain NPCCSS follow-up data.
- Capture of patient-reported outcomes is supported, but limited data have been captured, possibly due to lack of mobile application data capture capability.
- The EAP has provided arimoclomol expanded access to adult and pediatric patients, yielding maximum longitudinal data spanning greater than 2 years.

### Table 3: RWD collection - Assessment of 5-domain NPCCSS

| Domain | Ambulation | Fine Motor Skills | Swallow | Cognition | Speech |
|---|---|---|---|---|---|
| Scoring | **0:** Normal | **0:** Normal | **0:** Normal, no dysphagia | **0:** Normal | **0:** Normal |
| | **1:** Clumsy | **1:** Slight dysmetria/ dystonia (independent manipulation) | **1:** Cough while eating: *Intermittent dysphagia:* +1: w/Liquids[a] +1: w/Solids[a] *Dysphagia:* +2: w/Liquids[a] +2: w/Solids[a] | **1:** Mild learning delay, grade appropriate for age | **1:** Mild dysarthria (easily understood) |
| | **2:** Ataxic unassisted gait or not walking by 18 months | **2:** Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty) | | **3:** Moderate learning delay, individualized curriculum or modified work setting | **2:** Severe dysarthria (difficult to understand) |
| | **4:** Assisted ambulation or not walking by 24 months | **4:** Moderate dysmetria/ dystonia (limited fine motor skills, difficulty feeding self) | **4:** Nasogastric tube or gastric tube for supplemental feeding | **4:** Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function | **3:** Non-verbal/functional communication skills for needs |
| | **5:** Wheelchair dependent | **5:** Severe dysmetria/ Dystonia (gross motor limitation, requires assistance for selfcare activities) | **5:** Nasogastric tube or gastric tube feeding only | **5:** Minimal cognitive function | **5:** Minimal communication |
| **5DNPCCSS Total score = sum of individual domain scores, range: 0-25[b]** | | | | | |

[a] Score is additive (to "cough while eating"-score of 1) in subdomains 'intermittent dysphagia' and 'dysphagia' and can range from 0-5. Example: For intermittent dysphagia w/ solids and dysphagia w/ liquids a score of 4 applies (1+1+2)). [b] higher score = more severe clinical impairment.

## CONCLUSIONS

- **This collection of RWD from NPC patients participating in a global EAP will expand the understanding of this rare disease and the effectiveness and safety of arimoclomol.**
- **Addition of these RWD to the INPDR may help guide future clinical management and development of treatment options.**

**Acknowledgements:**

The successful design and setup of this EAP is the result of a collaborative effort involving many stakeholders, sites and staff including the INPDR.

A special thanks to Dr. Christina Guldberg for sharing her valuable insights and learnings in relation to this EAP.

**Disclosures:**

E. M. Berry-Kravis has worked under consultancy agreements for Zevra Therapeutics. D.Gallo is an employee of Zevra Therapeutics, K. Pagano and R.O'Reilly are in-house consultants with Zevra Therapeutics.

Poster prepared by Lene S Schmidt from Pharma IT Aps., funded by Zevra Therapeutics.