Poster 273

Long-term safety and effectiveness of arimoclomol adult and pediatric Niemann-Pick disease type C patients in the US early access program (EAP)

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BACKGROUND

- Niemann-Pick disease type C (NPC) is an ultra-rare, debilitating, progressive neurodegenerative, heterogenous lysosomal disease. The estimated incidence is ~1:100,000 live births.[1]
- Arimoclomol is the first treatment approved, in combination with miglustat, by the United States Food and Drug Administration (US FDA) to treat neurological manifestations of NPC based on positive safety and effectiveness results of the 12-month Phase 2/3 randomized, double-blind placebo-controlled interventional trial which enrolled 50 participants (age 2-18).
- An early access program (EAP) was launched to provide arimoclomol to patients with NPC in the US who were not eligible for or able to participate in clinical trials or who stopped receiving treatment from the open-label extension (OLE) study.
- The EAP provides real-world insights into safety and effectiveness in a broader age range of patients age 2 and above, including adults.

METHODS AND STATISTICS

- Data were handled in accordance with the Regulations (US Health Insurance Portability and Accountability Act of 1996 [HIPAA] and EU General Data Protection Regulation [GDPR]) and the treating physician obtained Institutional Review Board (IRB) approval.
- Treatment decisions and therapeutic strategies for patients with NPC were made independently of participation in the study; arimoclomol was provided by the Sponsor with prescribing dose based on participant's weight and Phase 2/3 study dosing regimen.
- Physicians reported demographics, medical history, physical exam/laboratory results, adverse events (AEs), weight, concomitant medications, arimoclomol dosing, and 5-domain NPC Clinical Severity Scale (5DNPCCSS) at baseline, with ongoing clinical assessments scheduled at months 4, 7 and 12 and subsequent routine visits thereafter (however, the visit schedule was not mandatory apart from the baseline).
- Effectiveness was measured as the change from baseline in the 5DNPCCSS and rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score.
  - The 5DNPCCSS is an NPC disease-specific validated measure of disease progression[2,3] based on the five most clinically relevant domains (cognition, speech, swallow, fine motor skills and ambulation) of the 17-domain NPCCSS.
  - The R4DNPCCSS removes the cognition domain and rescores the swallow domain from the 5DNPCCSS.[4]

RESULTS

Please see Poster 041 for details on overall group and Poster 193 for details about patients who completed multiple years of assessments.

Safety

- Fourteen (12.8%) participants overall had a total of 17 AEs by preferred terms (PTs) deemed related to arimoclomol; 8 (14.3%) pediatric group participants had 9 events and 6 (11.3%) adult group participants had 9 events.
- 3 (5.4%) participants in the pediatric group had 3 events and 2 (3.8%) adults had 2 events that led to discontinuation of arimoclomol.

Effectiveness – 5DNPCCSS and R4DNPCCSS

- Of 109 exposed participants, 100 (92%) had baseline 5DNPCCSS (**Figure 1**) and R4DNPCCSS analysis (**Table 2**).
- Results of 5DNPCCSS in the overall population remained relatively stable throughout the 4-year program with mean (SD; min, max) total score of 11.0 (6.15; 0, 25) at baseline and 12.0 (7.32; 2, 25) at Year 4 (Figure 1A).
  - Both pediatric (**Figure 1B**) and adult (**Figure 1C**) groups total scores fluctuated year to year but remained relatively stable overall; with the mean (SD; range) score of 10.1 [6.86; 0, 25] at baseline and 13.9 (9.88; 2, 25) at Year 4 in the pediatric group and 11.9 [5.17;1, 25] at baseline and 10.9 (5.53; 6, 22) at Year 4 in the adult group.
- Baseline mean (SD) R4DNPCCSS scores are shown in **Table 2**.

Table 1: Demographics and Treatment Characteristics of Participants in the Arimoclomol Early Access Program

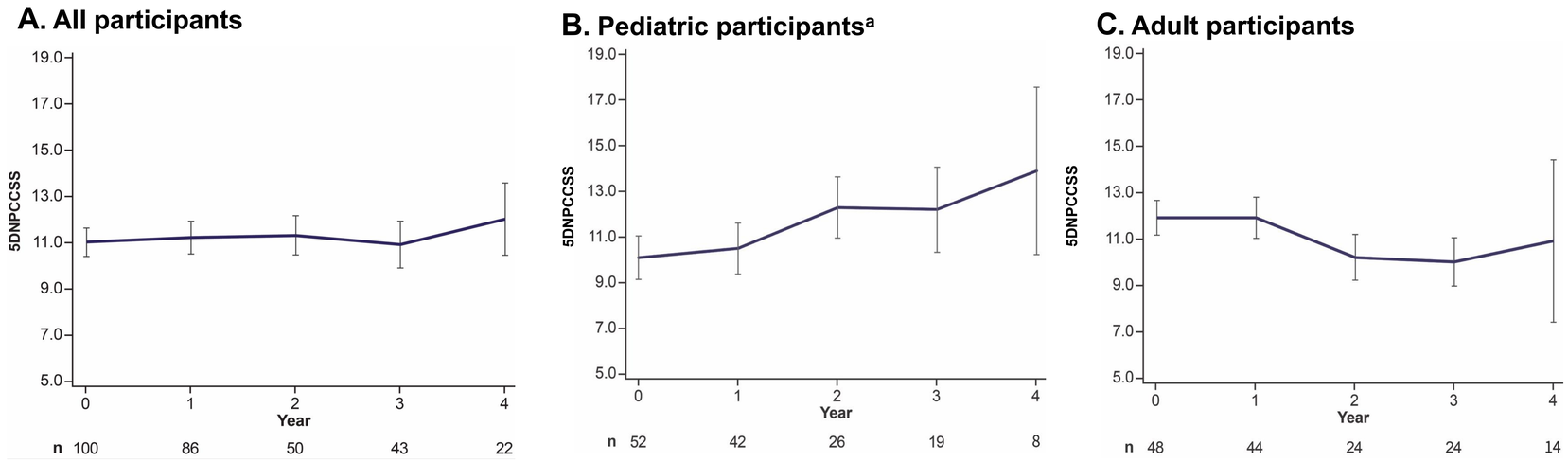
Demographic Variable Detail	Overall (N=109)	Pediatric (N=56)	Adult (N=53)
Gender – n (%)			
Male	57 (52.3)	29 (51.8)	28 (52.8)
Female	52 (47.7)	27 (48.2)	25 (47.2)
Miglustat use at treatment initiation – n (%)	57 (52.3)	30 (53.6)	27 (50.9)
Age at diagnosis (years)			
n	106	54	52
Mean (SD)	16.4 (13.0)	7.2 (4.6)	26.0 (11.9)
Median	12.0	8.0	24.8
Min, max	0.0, 62.0	0.0, 15.0	1.8, 62.0
Age at treatment initiation (years)			
n	109	56	53
Mean (SD)	19.9 (13.1)	9.4 (4.7)	31.1 (9.2)
Median	17.3	9.6	29.8
Min, max	2.0, 64.5	2.0, 17.8	18.0, 64.5
Duration of treatment with arimoclomol (days)*			
n	102	52	50
Mean (SD)	820 (539)	760 (536)	883 (541)
Median	836	735	937
Min, max	15, 1622	15, 1560	71, 1622

*Duration of exposure is defined as time on treatment from the date of treatment initiation to their final dose date of arimoclomol in the EAP.

Table 2: Summary of R4DNPCCSS Total Score (Exposed Participants)

Assessment	All Participants (N=109)	Pediatric (N=56)	Adult (N=53)
Treatment Initiation (Baseline)			
n	100	52	48
Mean (SD)	8.1 (4.98)	7.4 (5.56)	8.8 (4.20)
Median	7.0	6.0	8.5
Min, max	0, 20	0, 20	0, 20
Year 1			
n	86	42	44
Mean (SD)	8.2 (5.41)	7.6 (6.11)	8.7 (4.65)
Median	7.0	6.0	8.5
Min, max	0, 20	0, 20	0, 20
Year 2			
n	50	26	24
Mean (SD)	8.2 (4.95)	9.2 (5.81)	7.2 (3.68)
Median	7.0	9.0	7.0
Min, Max	0, 20	0, 20	0, 17
Year 3			
n	43	19	24
Mean (SD)	8.2 (5.53)	9.4 (6.69)	7.2 (4.32)
Median	7.0	11.0	5.5
Min, max	0, 20	0, 20	0, 17
Year 4			
n	22	8	14
Mean (SD)	9.0 (6.33)	10.6 (8.38)	8.1 (4.94)
Median	7.5	11.0	6.0
Min, max	1, 20	1, 20	3, 18

Figure 1: 5DNPCCSS Total Mean (SE) Score Over Time (Overall) by Group



[a] mean annualized disease progression is 1.5 in pediatric NPC patients[12]

DISCUSSION

- The EAP enrolled a broad range of participants representative of the heterogeneity in the NPC population,[1,5-8] including adults, a group underrepresented in clinical trials.
- Mean total 5DNPCCSS score fluctuated slightly from year to year but remained relatively stable throughout the duration of the program in the overall group and the adult participants.
  - While baseline disease severity based on 5DNPCCSS and R4DNPCCSS total scores was slightly higher in the adult group (11.9 [5.17] and 8.8 [4.20], respectively) compared to the pediatric group (10.1 [6.86] and 7.4 [5.56], respectively), results in the adult cohort showed more disease stability than in the pediatric cohort. This was as expected given the faster disease progression typically seen in pediatric onset NPC patients.[1,9]
  - Change in pediatric 5DNPCCSS total scores is consistent with results of the Phase 2/3 study[10,11] and remains below the mean annualized disease progression of 1.5 in the pediatric NPC patients.[12]
- Limitations of RWD collection include inconsistent reporting, quality of data collected, and biases such as selection bias.
- Limitations of this EAP and subgroup analysis include heterogeneity of NPC and a small total number of patients with data collected over the 4-year period.
- Lack of natural history data on disease progression in the adult NPC population limits the ability to extrapolate the impact of arimoclomol on disease severity and progression in the adult patient population.

CONCLUSIONS

- Arimoclomol was well tolerated. 5DNPCCSS scores were relatively stable in all age groups measured over the 4-year study period.
- The four years of adult data provides the most robust insights in this understudied NPC patient population and is the first published data on the impact of arimoclomol in the adult NPC patient population. The impact of treatment on the pediatric group is consistent with the results of the Phase 2/3 clinical trial and improves our understanding of the long-term outcomes with arimoclomol in a real-world clinical setting.

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