Background

Angelman syndrome (AS) is a rare neurodevelopmental condition with high motor and mental retardation and no known therapeutic options. It is a complex syndrome commonly diagnosed before the age of 5 years and characterized by intellectual disability, seizures, impaired speech, behavior, motor ataxia, and sleep disturbances. It is often characterized by a loss-of-function mutation in the UBE3A gene on chromosome 15 (85% of cases). The brain's normal development is altered in the update of maternal UBE3A allele expression. This results in reduced methylation of the paternal UBE3A allele (Figure 1). Reduced methylation of UBE3A expression results in decreased tonic inhibition, a presumed underlying neuropathology based on data from mouse models of AS.

RESULTS

Demographics

- 258 participants (121 per arm) completed the study.
- 186 participants had prior history of seizures.
- OV101 was administered adjunctively to concomitant and concomitant medications in AS, including benzodiazepines for five- to nine-pagers, antidepressants, antipsychotics, mood stabilizers, and antiepileptic.

Primary Endpoints: Safety and Tolerability

- A similar number of participants in the three treatment groups experienced AEs (p=0.60, OV101 QD vs placebo, and p=0.38, OV101 BID vs placebo).
- No events were noted in the OV101 QD treatment group (Table 2).
- Four participants discontinued treatment due to AEs:
  - OV101 BID (n=1, two events of seizures [possibly related])
  - OV101 QD (n=1, one event for myoclonus, seizures, and incontinence/seizure disorder)
  - placebo (n=2).

Exploratory Efficacy: CGI-I Response at Week 12

- CGI-I response defined as at least a 3-category improvement compared to placebo and rated “much improved” or “very much improved” on the Overall Clinical Impression Scale.
- There was no significant difference in response to any treatment arm (p=0.2646).

CONCLUSIONS

- OV101 was well tolerated with no new safety or serious AEs.
- The reported AEs were mild, and discontinuations due to AEs were low.
- No serious AEs were reported.
- The OV101 exploratory efficacy endpoint using CGI-I suggested a global improvement level, observed at week 12 with OV101 QD vs placebo (p=0.0340).
- OV101 QD showed improvement in latency to sleep compared with placebo, as measured by caregiver’s report.
- The PGI suggested that a clinically meaningful improvement in CGI-I was correlated with improvements in communication, challenging behavior, and anxiety.
- The PEDI-CAT Mobility and Daily Activity Summary Scores in the OV101 QD group showed improvements compared with placebo.
- Improvement was observed in the Disability Index of CHAQ as well as the PEDI-CAT Mobility and Daily Activity Summary Scores in OV101 QD group compared with placebo (p=0.0406 and n=24; LS mean, -5.79; SE, 2.162; P=0.0406) compared with placebo (n=24; LS mean, 9.68; SE, 3.271; P=0.0406) compared with placebo.
- Significant improvements were noted in the Disability Index of CHAQ as well as the PEDI-CAT Mobility and Daily Activity Summary Scores in OV101 QD group compared with placebo (p=0.0340, respectively).

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