Electronic Seizure Diary Compliance In An Adult Focal Epilepsy Clinical Trial

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BACKGROUND

- Clinical trials in epilepsy typically measure seizure frequency and type as the primary outcome to assess efficacy of a therapy. Paper diaries have typically been used for seizure documentation. Handheld electronic devices are increasingly more accessible and offer several advantages in terms of ease of use in recording and tracking of seizures, timeliness of data and ability to provide immediate feedback.
- We are developing XEN1101, a novel voltage-gated potassium (Kv7.2/3) channel opener, for the treatment of epilepsy. In the recently completed X-TOLE phase 2 clinical study (Fig 1) in adults with focal onset seizures (FOS) (NCT03796962), median percent reductions in monthly FOS frequency were [52.8%] in the XEN1101 25 mg group (p<0.001), [46.4%] in the XEN1101 20 mg group (p<0.001) and [33.2%] in the XEN1101 10 mg group (p=0.035) compared to [18.2%] in the placebo group.
- The assessment of efficacy in an adult FOS clinical trial using an electronic seizure diary (eDiary) instead of a paper diary was explored, following on from the successful use of an eDiary in pediatric epilepsy clinical trials. In this analysis, we determined the overall compliance and the impact of select clinical factors (e.g. duration of epilepsy, seizure type, and AEDs) in the X-TOLE study and reviewed the potential benefits of utilizing an eDiary for adult FOS trials.

METHODS

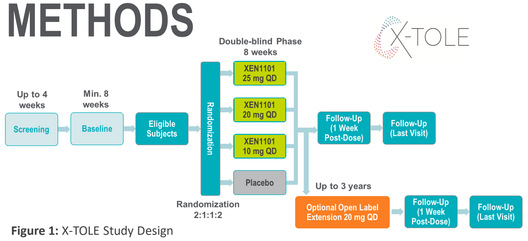

Figure 1: X-TOLE Study Design

Key Inclusion Criteria:

- Patients aged 18-75 years (inclusive) with an International League Against Epilepsy [ILAE][1] diagnosis of focal epilepsy (≥ 2 years).
- Treatment with a stable dose of 1 to 3 allowable current antiepileptic drugs (AEDs) for at least one month prior to screening, during baseline, and throughout the double-blind period (DBP).
- Ability to keep accurate seizure diaries.

Key Additional Eligibility Criteria (for randomization):

- ≥ 4 focal onset seizures per month (28 days) recorded with an eDiary during the planned 8-week baseline period.
- eDiary completed with a minimum compliance of 80%, of all days (i.e., ≥ 45 days) during the 8-week baseline period.
- Patients should not be seizure-free for more than 21 consecutive days during baseline period.

- A custom eDiary (Fig 2) was developed and used in X-TOLE, a randomized, double-blind, placebo-controlled, multicenter study of XEN1101 as adjunctive therapy in adult patients with focal onset epilepsy. The eDiary stored daily seizure and treatment compliance information which was transmitted to the database by wifi or cellular network.
- Data were analyzed from the baseline period* and the subsequent randomized DBP (56 days).
- Central surveillance of eDiary functionality and compliance was utilized to inform participating sites of their subjects' status, enabling them to provide feedback in real time.
- Seizure counts could only be entered in the eDiary on the day after their occurrence, until up to 3 retrospective days.
- The eDiary was used as the primary source for seizure related efficacy data. A paper backup diary was introduced by protocol amendment to allow temporary data entry only, in the event of documented technical issues encountered with the eDiary.

Figure 2: Sample eDiary Screen Captures

Table 1: Focal Onset Seizure Types

	Seizure Description
Type 1	Focal aware seizures with motor signs
Type 2	Focal seizures with impaired awareness with motor signs
Type 3	Focal seizures with impaired awareness with NO motor signs
Type 4	Focal seizures that lead to generalized tonic-clonic seizures
Type 5	Focal aware seizures with NO motor signs

- eDiary compliance was defined as the total number of days with any entry out of the total number of days per study phase (baseline or DBP) assessed by evaluation of the database.
- Subjects reported all focal onset seizures by type (Table 1). Seizure counts for endpoint analysis were based on countable focal seizures Types 1-4. Subjects were required to perform eDiary input themselves, with assistance for event recall permitted, if needed. Type 4 seizures were analyzed to determine if having severe seizures with loss of consciousness impacted compliance.

*Due to the global COVID pandemic, if in-person visits had to be delayed, subjects were permitted to continue in baseline up to a maximum of 140 days (per protocol amendment) until the required in-person randomization visit could take place. The additional eligibility requirements for randomization (e.g. ≥ 4 focal onset seizures per 28 days) was assessed over the first 56 days and it was determined whether the baseline could continue until an in-person visit could be performed. In these subjects, the additional eligibility criteria had to be maintained throughout the extended baseline in order to randomize.

Table 2: Demographics and Baseline Characteristics of mITT Population

Characteristic		Placebo (N = 114)	XEN1101 10mg (N = 46)	XEN1101 20mg (N = 51)	XEN1101 25mg (N = 112)
Age, Mean (SD)		42.9 (13.7)	40.0 (12.1)	41.7 (13.6)	38.4 (13.0)
Sex, n (%)	Female	61 (54)	27 (59)	26 (51)	53 (47)
	Male	53 (46)	19 (41)	25 (49)	59 (53)
Region, n (%)	North America	47 (41)	15 (33)	19 (37)	46 (41)
	Europe	67 (59)	31 (67)	32 (63)	66 (59
Age of Onset, Mean (SD)		19.2 (14.7)	19.8 (14.8)	14.1 (12.1)	15.4 (12.2)
Baseline Seizure Frequency (Monthly)	Mean (SD)	27.3 (38.5)	34.5 (40.9)	29.0 (42.0)	22.3 (27.0)
	Median	13.4	17.4	14.5	12.8
Type 4 Seizure, n (%)	Reported	33 (29)	10 (22)	15 (29)	27 (24)
	Not Reported	81 (71)	36 (78)	36 (71)	85 (76)
Number of AEDs Taken in Baseline, n (%)	1	12 (11)	4 (9)	2 (4)	11 (10)
	2	46 (40)	18 (39)	20 (39)	46 (41)
	3	56 (49)	24 (52)	29 (57)	55 (49)

RESULTS

- Of 530 potential patients screened, 329 were randomized, 323 subjects were treated and provided seizure data (mITT population, Table 2), and 285 completed the study (N = 109 placebo; N = 45 at 10mg XEN1101; N = 43 at 20mg XEN1101; N= 88 at 25mg XEN1101).
- The median (range) duration of the baseline period was 58.0 (53-139) days in the mITT population. During baseline 18997 daily seizure entries were recorded, eDiary compliance was 95.5 ± 7.0% (mean ± SD) and median compliance was 98.4%. No significant differences were found in compliance between males and females during the baseline period, with a mean compliance of 95.2 and 95.8% respectively (Fig 3).
- An unexpected opportunity to explore the flexibility and utility of an eDiary was presented by the occurrence of the global COVID pandemic. The eDiary had a capability of capturing 200 days, allowing for subjects to record a baseline period of up to 140 days in case of COVID related site access restrictions. Thirty-two subjects thus had an extended baseline period of 67-139 days (Fig 3).

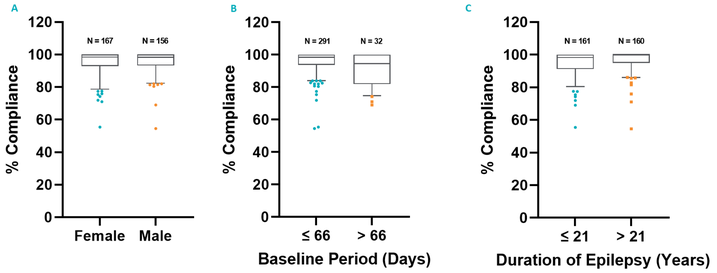

Figure 3: Box and whisker plot with median, interquartile range and 5-95th percentiles, showing eDiary compliance during the baseline period for the mITT population comparing sex (A); planned baseline period vs. extended baseline of > 66 days (B); and epilepsy duration, ≤ 21 years and >21 years (C). The median duration of epilepsy was 21 years.**

- For randomized subjects, there were a total of 15941 daily seizure recordings in the eDiary during the DBP.
- A total of 285 subjects completed the 8-weeks randomized DBP, eDiary compliance during this period was maintained at 94.4 ± 8.7% (mean ± SD) and median compliance was 98.2%. No differences were found in the compliance between the baseline and DBP, each with a mean compliance of 95.4 and 94.4% respectively, and no differences were found between the treatment groups (Fig 6). No significant differences were found in the DBP compliance between regions, or by number of AEDs (taken at baseline) (Fig 6 and 7).
- At least one paper backup daily diary entry was used by 26 subjects that completed the DBP.
- The data show that good eDiary compliance can be achieved in randomized clinical trials in adult focal onset epilepsy.

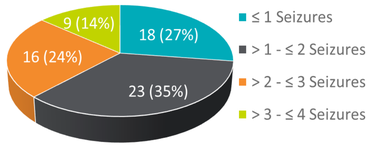

Figure 4: Analysis of subjects that recorded less than the protocol-specified minimum of 4 focal onset seizures per 28 days. Data displayed as n (%) of subjects per category by monthly seizure rate.

Figure 5: Venn diagram shows the number of subjects (N = 95) who failed to meet additional eligibility criteria for randomization: ≥ 4 focal onset seizures per 28 days on average, eDiary completion of a minimum of 80%, and not being seizure-free for more than 21 consecutive days during the baseline period, including overlapping and non-overlapping results (A); remainder of subjects (N = 29) who did not randomize for additional reasons, "other" included protocol violations (B).

B

Additional reasons	N
Lost to follow-up	3
Withdrawal	9
Other	17

- There were 124 subjects who entered baseline, but failed to be randomized, mainly for the following reasons: 20 subjects failed baseline due to not maintaining a minimum of 80% eDiary compliance, and 66 subjects recorded less than the protocol-specified minimum of 4 focal onset seizures per 28 days, and 84 subjects had >21 consecutive days without a seizure during baseline (values may overlap) (Fig 4).
- There were over 6000 daily seizure recordings entered in the eDiary during baseline for subjects who failed to randomize.
- Of the 66 subjects that recorded less than 4 focal onset seizures per 28 days, 86% had ≤ 3 seizures per month (Fig 5).

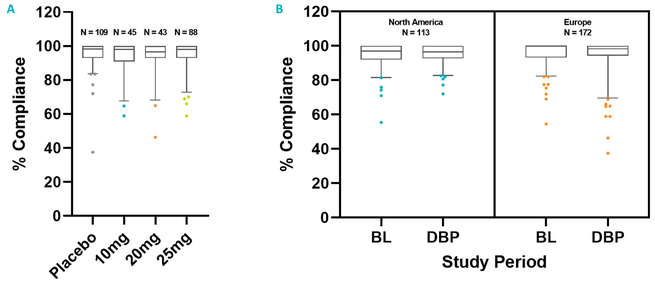

Figure 6: Box and whisker plot with median, interquartile range and 5-95th percentiles, showing eDiary compliance for subjects that completed the DBP, comparing treatment groups during the DBP (A); and regions for BL and DBP (B).**

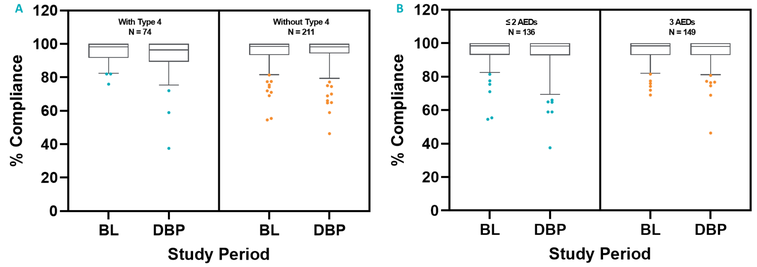

Figure 7: Box and whisker plot with median, interquartile range and 5-95th percentiles, showing eDiary compliance for subjects that completed the DBP, comparing with and without reported Type 4 seizures (A); and number of antiepileptic drugs (AEDs) taken (B) during BL and DBP.**

**Subjects were permitted to use paper back-up to supplement the eDiary entries on days when verified technical problems arose with the eDiary (% non-missing daily eDiary entries only presented, supplemental paper back-up data not shown).

CONCLUSIONS

- Over the conduct of the study, there were over 42000 daily seizure recordings entered in the eDiary.
- We learned that high eDiary compliance could be maintained in adults with focal onset epilepsy, aided by central monitoring in real time. The eDiary helped to maintain a strong connection to the subject's clinical status and enabled rigorous assessment of eligibility for randomization to enable progression through the study with accurate data capture.
- Although paper diaries have been used in a majority of epilepsy clinical trials for seizure documentation there are possible limitations, including a lack of data entry over an extended window between clinic visits, illegible data entries, no timestamps for data entries, and the inability to monitor data entries in real time.[2] Recently completed adult FOS trials that utilized paper diaries for seizure documentation had a placebo response range from 21.5-37.7%.[3-5] The use of the eDiary in X-TOLE may have contributed to the relatively low placebo response (18.2%).
- Based on the results of this compliance analysis, we believe eDiaries may set a new standard for adult FOS studies.

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