SUPPLEMENTARY MATERIAL

Effectiveness and safety of adjunctive cenobamate in people with focal-onset epilepsy: evidence from the first interim analysis of the BLESS Study

Authors

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SUPPLEMENTARY 1

LIST OF SITES AND INVESTIGATORS PARTICIPATING ON BLESS STUDY GROUP

updated on June 30th, 2023 (date of database extraction for the First Interim Statistical Analysis)

Alfredo D'Aniello (IRCCS Neuromed, Pozzilli - IS, Italy); Cecilia Catania, Alessandra Morano, Biagio Orlando (Department of Human Neurosciences, Policlinico Umberto I, Rome, Italy); Angela La Neve, Teresa Francavilla, Francesca Pia Mazzeo (AOU Consorziale Policlinico-Centro Epilessia, Neurologia Amaducci, Bari, Italy); Giada Pauletto, Marco Belluzzo, Anna Carmen Nilo (ASU FC-SOC Neurologia, Udine, Italy); Alessia Peretti, Diana Polo, (Regional Adult Epilepsy Center, Neurology Unit, San Bortolo Hospital, Vicenza, Italy); Giulia Lippa, Marianna Nesta, Lorenzo Ricci (Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico, Rome, Italy); Alberto Danieli, Elisa Osanni (Epilepsy and Clinical Neurophysiology Unit, IRCCS Eugenio Medea, Scientific Institute, Conegliano - TV, Italy); Francesco Fortunato, Giuseppe Magro, Laura Marino, Ilaria Sammarra (Institute of Neurology, University Magna Graecia, Catanzaro, Italy); Carlo Andrea Galimberti, Domenico Lomonaco (Epilepsy Center, IRCCS Mondino Foundation, Epilepsy Center, IRCCS Mondino Foundation, ERN EpiCare full member, Pavia, Italy); Pietro Pignatta, Devis Collura, Emanuela Viglietta (Humanitas Gradenigo-SS Neurologia, Turin, Italy).

SUPPLEMENTARY 2

STUDY OBJECTIVES

(according to BLESS Study Protocol version 2.0 of May 5th, 2023)

Primary objective

To describe the effectiveness of adjunctive cenobamate treatment in adult patients with uncontrolled focal epilepsy in Italy, overall and according to age class, setting of cenobamate treatment, cenobamate final target daily dose prescribed, and number of concomitant ASMs.

This was assessed by intra-patient percent change and achievement of a ≥50% reduction in the seizure frequency from the pre-treatment baseline over a period of 52 weeks.

Secondary objectives

1. To describe the effectiveness of adjunctive cenobamate treatment in adult patients with uncontrolled focal epilepsy in Italy, as assessed by achievement of (i) a ≥75%/≥90%/=100% reduction, and (ii) a ≥50%/≥75%/≥90%/=100% sustained reduction in the seizure frequency from the pre-treatment baseline over a period of 52 weeks.

2. To describe the safety and tolerability of cenobamate as adjunctive treatment in adult patients with uncontrolled focal epilepsy in a real-world setting in Italy.

3. To describe the 52-week treatment retention with cenobamate in adult patients affected by uncontrolled focal epilepsy in a real-world setting in Italy.

4. To describe the Health-Related Quality of Life (HRQoL) status of patients treated with cenobamate in a real-world setting in Italy, by means of the 31-item Quality Of Life In Epilepsy inventory (QOLIE-31) at 12, 24, and 52 weeks from treatment initiation.

5. To describe global functioning, sleepiness, anxiety, and depression of patients treated with cenobamate in a real-world setting in Italy, by means of the Clinical Global Impression (CGI) scales, the Epworth Sleepiness Scale (ESS), and the Hospital Anxiety and Depression Scale (HADS) at 12, 24, and 52 weeks from treatment initiation.

Explorative objective

To further describe the effectiveness of adjunctive cenobamate treatment in adult patients with uncontrolled focal epilepsy in Italy at 76 and 104 weeks, where available.

EFFECTIVENESS OUTCOMES DEFINITION

(according to BLESS Study Protocol version 2.0 of May 5th, 2023)

Monthly seizure frequency during the pre-treatment baseline and the post-baseline assessments is calculated by summing the total number of seizures (all types of seizures) reported in each considered period and dividing by the duration of that period (number of days), excluding days with no available data, and multiplying by 28 to normalize to a monthly rate.

At pre-treatment baseline, monthly seizure frequency is calculated based on the number of seizures experienced during the previous 12 weeks with respect to the index date. At post-baseline assessment time-points, monthly seizure frequency is based on the number of seizures experienced since the index date (i.e., during the previous 12 weeks for the 12-week assessment, during the previous 24 weeks for the 24-week assessment, and during the previous 52 weeks for the 52-week assessment).

Intra-patient percent change from baseline is calculated as [(monthly seizure frequency at post-baseline assessments - monthly seizure frequency at baseline), divided by the monthly seizure frequency at baseline] multiplied by 100.

Patients achieving a ≥50%/≥75%/≥90%/=100% seizure reduction and sustained reduction in the seizure frequency from the pre-treatment baseline, evaluated at 12, 24, 52 weeks (and at 76 and 104 weeks where available) of cenobamate treatment initiation were evaluated.

Seizure freedom is defined as seizure frequency of zero (=100% seizure reduction) at each above specified assessment time-point.

Sustained seizure frequency reduction is defined as a reduction in baseline seizure frequency achieved at 12 weeks of cenobamate treatment initiation, that continues (is sustained) without interruption and without cenobamate permanent discontinuation through the observation period until 24 and 52 weeks of cenobamate treatment initiation.

SAMPLE SIZE JUSTIFICATION

(according to BLESS Study Protocol version 2.0 of May 5th, 2023)

The sample size of 1200 patients was defined according to feasibility considerations with respect to both the enrolment period duration and the number of participating sites.

In order to provide the precision estimate basing on such sample sizes, we considered the findings of a post-hoc analysis of the C021 multicenter, open-label study (ClinicalTrials.gov Identifier: NCT02535091) published by Sperling et al. (1). Based on feasibility study assessment and literature search, it is reasonable to expect that about 10% of enrolled patients will be derived from the Italian Compassionate Use Program (CUP), about 27% might be treated with >2 ASMs concomitant with cenobamate and up to 50% with a cenobamate target daily dose of 200 mg (1-2). No literature from routine practice is available on the portion of subjects aged 65 and over to determine the expected size for this subgroup.

In addition, considering an estimated retention rates with cenobamate of 80% at 1 year and 72% at 2 years [Sander et al., 2022], we expect that up to 20% of the enrolled patients could be not evaluable for the primary analysis (due to failure in meeting the eligibility criteria, or to non-available long-term data).

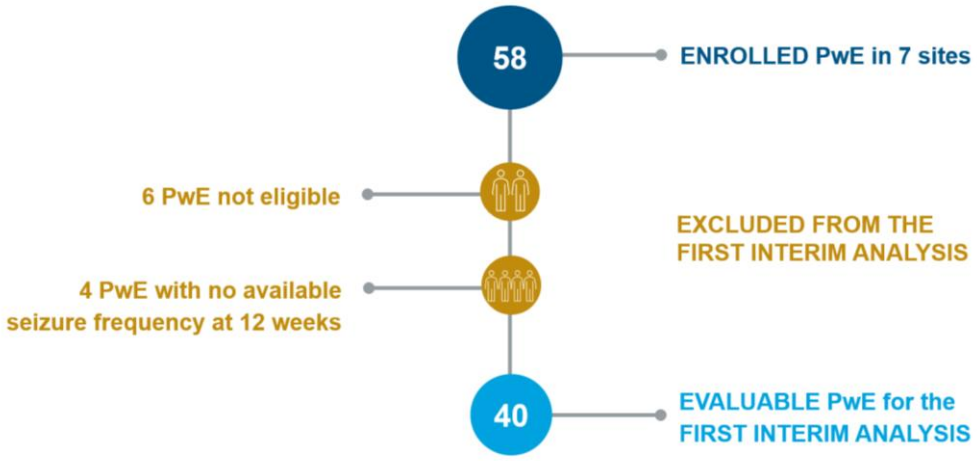
Therefore, considering a target sample size of 1200 we expect 960 patients evaluable for overall primary analysis, and between 96 and 480 patients evaluable for primary analyses in the smallest subgroups. The table S1 reports the 95% Confidence Interval (CI) estimations for the expected proportions of patients achieving a ≥50% reduction in the seizure frequency from the pre-treatment baseline, calculated over consecutive 6-month intervals during the treatment maintenance phase when the sample sizes are 960 (overall primary analysis), 480, 260 and 96 (stratified primary analyses), under the assumption that the CI is based on the normal approximation (3).

Table S1. 95% Confidence Interval estimations according to different assessment time-points and sample sizes for overall (N=960) and stratified (N=480, N=260, N=96) BLESS Study primary analyses

6-month intervals of response evaluation during the treatment maintenance phase	Expected proportion of patients achieving a ≥50% reduction in the seizure frequency	N	95% CI
Months 3-9	71.5%	960	68.6%-74.4%
		480	67.5%-75.5%
		260	66.0%-77.0%
		96	62.5%-80.5%
Months 9-15	73.6%	960	70.8%-76.4%
		480	69.7%-77.5%
		260	68.2%-79.0%
		96	64.8%-82.4%

CI: confidence interval.

Figure S1. BLESS Study patient disposition of interim analysis



At the time of data extraction, 7 out of 50 planned sites were fully authorized for enrollment and data collection.
PwE: people with epilepsy.

REFERENCE FOR SUPPLEMENTARY 2 INFORMATION

1. Sperling MR, Abou-Khalil B, Aboumatar S, et al., Efficacy of cenobamate for uncontrolled focal seizures: Post hoc analysis of a Phase 3, multicenter, open-label study. Epilepsia. 2021;62(12):3005-15.
2. Lattanzi S, Trinka E, Zaccara G, Striano P, Del Giovane C, Silvestrini M, Brigo F. Adjunctive Cenobamate for Focal-Onset Seizures in Adults: A Systematic Review and Meta-Analysis. CNS Drugs. 2020 Nov;34(11):1105-20.
3. Dixon WJ, Massey FJ. Introduction to Statistical Analysis. 4th Edition McGraw-Hill. 1983; 80-5, 105-7.

SUPPLEMENTARY 3

LIST OF ETHICS COMMITTEES THAT EVALUATED THE BLESS STUDY

updated on June 30th, 2023 (date of database extraction for the First Interim Statistical Analysis)

Table S2. List of ethics committees and relevant clinical sites of the BLESS Study

EC name	Study Site name and city	Study Site number	EC evaluation date
Comitato Etico IRCCS Istituto Neurologico Mediterraneo Neuromed	IRCCS Neuromed, Pozzilli (IS), Italy	01	29/09/2022
Comitato Etico dell'Università Sapienza	Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy	02	23/11/2022
Comitato Etico Indipendente A.O.U. Consorziale Policlinico	AOU Consorziale Policlinico-Centro Epilessia, Neurologia Amaducci, Bari, Italy	03	08/02/2023
Spettabile Comitato Etico per le Sperimentazioni Cliniche della Provincia di Vicenza	Regional Adult Epilepsy Center, Neurology Unit, San Bortolo Hospital, Vicenza, Italy	07	11/10/2022
Comitato Etico Fondazione Policlinico Campus Bio-Medico	Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico, Rome, Italy	08	20/09/2022
Comitato Etico per la Sperimentazione Clinica Provincia di Treviso e Belluno	Epilepsy and Clinical Neurophysiology Unit, IRCCS Eugenio Medea, Scientific Institute, Conegliano (TV), Italy	09	23/02/2023
Comitato Etico Regione Calabria Area Centro c/o A.O.U. Mater Domini	Institute of Neurology, University Magna Graecia, Catanzaro, Italy	10	15/09/2022
Comitato Etico Pavia c/o IRCCS Policlinico San Matteo	Epilepsy Center, IRCCS Mondino Foundation, ERN EpiCare full member, Pavia, Italy	11	07/02/2023

EC name	Study Site name and city	Study Site number	EC evaluation date
Comitato Etico Interaziendale AOU Città della Salute e della Scienza	Humanitas Gradenigo-SS Neurologia, Turin, Italy	13	12/12/2022

EC: ethics committee.