


# Validated outcome of treatment changes according to International League Against Epilepsy criteria in adults with drug-resistant focal epilepsy

Marco Mula<sup>1</sup>  | Gaetano Zaccara<sup>2</sup> | Carlo Andrea Galimberti<sup>3</sup> | Bruno Ferrò<sup>4</sup> | Maria Paola Canevini<sup>5</sup> | Addolorata Mascia<sup>6</sup> | Oriano Mecarelli<sup>7</sup> | Roberto Michelucci<sup>8</sup> | Laura Rosa Pisani<sup>9</sup> | Luigi Maria Specchio<sup>10</sup> | Salvatore Striano<sup>11</sup> | Emilio Perucca<sup>12</sup>

<sup>1</sup>Institute of Medical and Biomedical Education, St George's University of London and Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals National Health Service Foundation Trust, London, UK

<sup>2</sup>Regional Health Agency of Tuscany, Florence, Italy

<sup>3</sup>C. Mondino National Neurological Institute, Pavia, Italy

<sup>4</sup>UCB Pharma, Milan, Italy

<sup>5</sup>Department of Health Sciences, University of Milan, Epilepsy Center, San Paolo Hospital, Milan, Italy

<sup>6</sup>IRCCS Neuromed, Pozzilli, Italy

<sup>7</sup>Department of Human Neurosciences, Sapienza University, Rome, Italy

<sup>8</sup>IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neurologia Ospedale Bellaria, Bologna, Italy

<sup>9</sup>Neurology Unit, Cutrona-Zodda Hospital, Barcellona Pozzo di Gotto, Italy

<sup>10</sup>University of Foggia, Foggia, Italy

<sup>11</sup>Department of Neuroscience and Reproductive and Odontostomatological Sciences, School of Medicine, Federico II Epilepsy Center, University of Naples, Naples, Italy

<sup>12</sup>Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia and Clinical Trial Center, IRCCS Mondino Foundation, Pavia, Italy

## Correspondence

Marco Mula, Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, UK.  
Email: mmula@sgul.ac.uk

## Funding information

UCB Pharma

## Summary

**Objective:** Although many studies have attempted to describe treatment outcomes in patients with drug-resistant epilepsy, results are often limited by the adoption of non-homogeneous criteria and different definitions of seizure freedom. We sought to evaluate treatment outcomes with a newly administered antiepileptic drug (AED) in a large population of adults with drug-resistant focal epilepsy according to the International League Against Epilepsy (ILAE) outcome criteria.

**Methods:** This is a multicenter, observational, prospective study of 1053 patients with focal epilepsy diagnosed as drug-resistant by the investigators. Patients were assessed at baseline and 6, 12, and 18 months, for up to a maximum of 34 months after introducing another AED into their treatment regimen. Drug resistance status and treatment outcomes were rated according to ILAE criteria by the investigators and by at least two independent members of an external expert panel (EP).

**Results:** A seizure-free outcome after a newly administered AED according to ILAE criteria ranged from 11.8% after two failed drugs to 2.6% for more than six failures. Significantly fewer patients were rated by the EP as having a “treatment failure” as compared to the judgment of the investigator (46.7% vs 62.9%,  $P < 0.001$ ), because many more patients were rated as “undetermined outcome” (45.6% vs 27.7%,  $P < 0.001$ ); 19.3% of the recruited patients were not considered drug-resistant by the EP.

**Significance:** This study validates the use of ILAE treatment outcome criteria in a real-life setting, providing validated estimates of seizure freedom in patients with drug-resistant focal epilepsy in relation to the number of previously failed AEDs. Fewer than one in 10 patients achieved seizure freedom on a newly introduced AED over the study period. Pseudo drug resistance could be identified in one of five cases.

#### KEYWORDS

antiepileptic drugs, drug-resistant epilepsy, epilepsy, outcome, treatment

## 1 | INTRODUCTION

Over the past 35 years, several authors have focused on treatment outcomes in epilepsy. Early studies,<sup>1,2</sup> followed by more recent ones,<sup>3–7</sup> attempted to associate the probability of becoming seizure-free with the number of antiepileptic drugs (AEDs) that previously failed for the patient. However, many of these studies have methodological limitations, such as a short follow-up period, retrospective design, the use of different definitions/criteria for drug-resistant epilepsy, and most importantly, different definitions of seizure freedom.<sup>8–10</sup> It is, therefore, important to adopt homogenous criteria to establish whether a specific AED was successful or ineffective.

In 2010, an ad hoc task force of the International League Against Epilepsy (ILAE) proposed a new definition of drug-resistant epilepsy.<sup>11</sup> The novelty of this definition is the two hierarchical levels for AED response, with Level 1 categorizing outcomes of each therapeutic intervention and Level 2 providing a core definition of drug-resistant epilepsy based on how many informative AED trials resulted in treatment failure. The new definition also highlights the “pseudo drug resistance” phenomenon, where patients are erroneously labeled as drug-resistant.<sup>8,12</sup> The ILAE document also includes a formal definition of seizure freedom that requires a seizure-free period of either 12 months or three times the longest interseizure interval experienced prior to starting the intervention, whichever is longer. Based on this background, the present study was designed with the aim of investigating clinical response to a newly introduced AED in adults with drug-resistant focal epilepsy, as defined by the new ILAE criteria, with clinical response for each individual patient categorized independently by the investigator (treating physician) and by an external expert panel (EP).

#### Key Points

- This study supports the validity of the ILAE treatment outcome criteria in clinical practice
- This study provides validated estimates of seizure freedom in patients with drug-resistant focal epilepsy in relation to the number of previously failed AEDs
- Fewer than one in 10 patients with drug-resistant focal epilepsy achieve seizure freedom on a newly introduced AED
- One of five patients presents pseudo drug-resistant focal epilepsy

## 2 | MATERIALS AND METHODS

### 2.1 | Study design, protocol approvals, registrations, and patient consent

This is a multicenter, observational, prospective study of adults with drug-resistant focal epilepsy recruited at 43 epilepsy centers in Italy between 2011 and 2015 (Prometeo Study SP0992). The study was approved by ethics committees at all participating sites, and written informed consent was obtained from all participants (or guardians of participants). The study was registered in the Italian Medicines Agency (AIFA) public register for observational studies, and the identifier number was SP0992. A copy of the protocol can be requested from the AIFA register for observational studies at [info\\_rso@aifa.gov.it](mailto:info_rso@aifa.gov.it).

### 2.2 | Study population

Patients were enrolled consecutively according to the following inclusion criteria: (1) age  $\geq 18$  years; (2) established diagnosis of epilepsy with focal seizures with or without

bilateral tonic-clonic seizures; (3) uncontrolled seizures on current AED treatment, meeting ILAE criteria for drug-resistant epilepsy<sup>11</sup>; (4) clinical need to modify existing treatment by introducing another AED, either as an add-on or in substitution, and in a combination not previously used; (5) longest interseizure interval not exceeding 6 months in the 12 months preceding enrollment; (6) ability to reliably complete a seizure diary and to adhere to the protocol; and (7) willingness to provide written informed consent. Patients were excluded if they (1) were scheduled for epilepsy surgery or vagus nerve stimulation, (2) had primary generalized seizures, (3) had a history of psychogenic nonepileptic seizures or any other potential seizure mimics, (4) had a severe medical illness or short life expectancy, or (5) were participating in clinical trials.

Patients were followed prospectively and assessed at time 0 (baseline, just before introduction of another AED) and at 6, 12, and 18 months, or more frequently if clinically indicated. An additional visit was scheduled for patients who had been seizure-free for at least 2 months (60 days) at the 18-month visit, but who had not yet met ILAE criteria for seizure freedom. In these patients, the additional visit could be performed up to 16 months after the 18-month visit, to provide sufficient time to establish whether seizure freedom had been achieved. Therefore, the maximum period of observation between time 0 and the last visit was 34 months (148 weeks). All medications were used according to standard practice, as considered appropriate by the treating physician. Adjustments in dosage of the newly introduced AED and of concomitant drugs were allowed at any time during the study at the discretion of the physician. The study was conducted according to Good Clinical Practice guidelines. All data were recorded in electronic case report forms (eCRFs). Recorded information included demographic and disease-related characteristics, and treatment details (dose schedules, titration rates, serum drug concentrations, and clinical response) for each AED and for other drugs used by the patient in the past and during the duration of the trial.

### 2.3 | Study outcome

The primary end point of the study was clinical response to the newly introduced AED. The response status was categorized by the investigator as seizure freedom, treatment failure, or undetermined according to ILAE criteria.<sup>11</sup> Specifically, seizure freedom refers to absence of seizures for a period of at least 12 months or three times the longest preintervention interseizure interval, whichever is longer; treatment failure refers to occurrence of any seizure during the observation period, provided that the introduced AED had been used appropriately and adequately. “Undetermined” refers to outcomes that did not fit with any of the previously mentioned categories.

At the end of the follow-up period, all patient data entered in the eCRFs were reviewed independently by two members of an ad hoc EP (Table S1) to (1) confirm or refute the patient's drug-resistant status at enrollment, (2) confirm whether the use of the newly introduced AED was appropriate and adequate, and (3) confirm or refute the categorization of treatment outcome given by the investigator. EP members were selected according to their curricula vitae and documented expertise in epilepsy. Each individual patient's eCRFs were assigned to two members of the EP by an automated computerized system in a randomized and blinded manner, while ensuring that reviewers did not receive eCRFs for patients enrolled at their own institution. In case of disagreement, the two reviewers were unblinded and were asked to communicate to resolve the disagreement. If the disagreement was not resolved, the EP chair evaluated the reviewers' positions and made the final decision on the patient's response category.

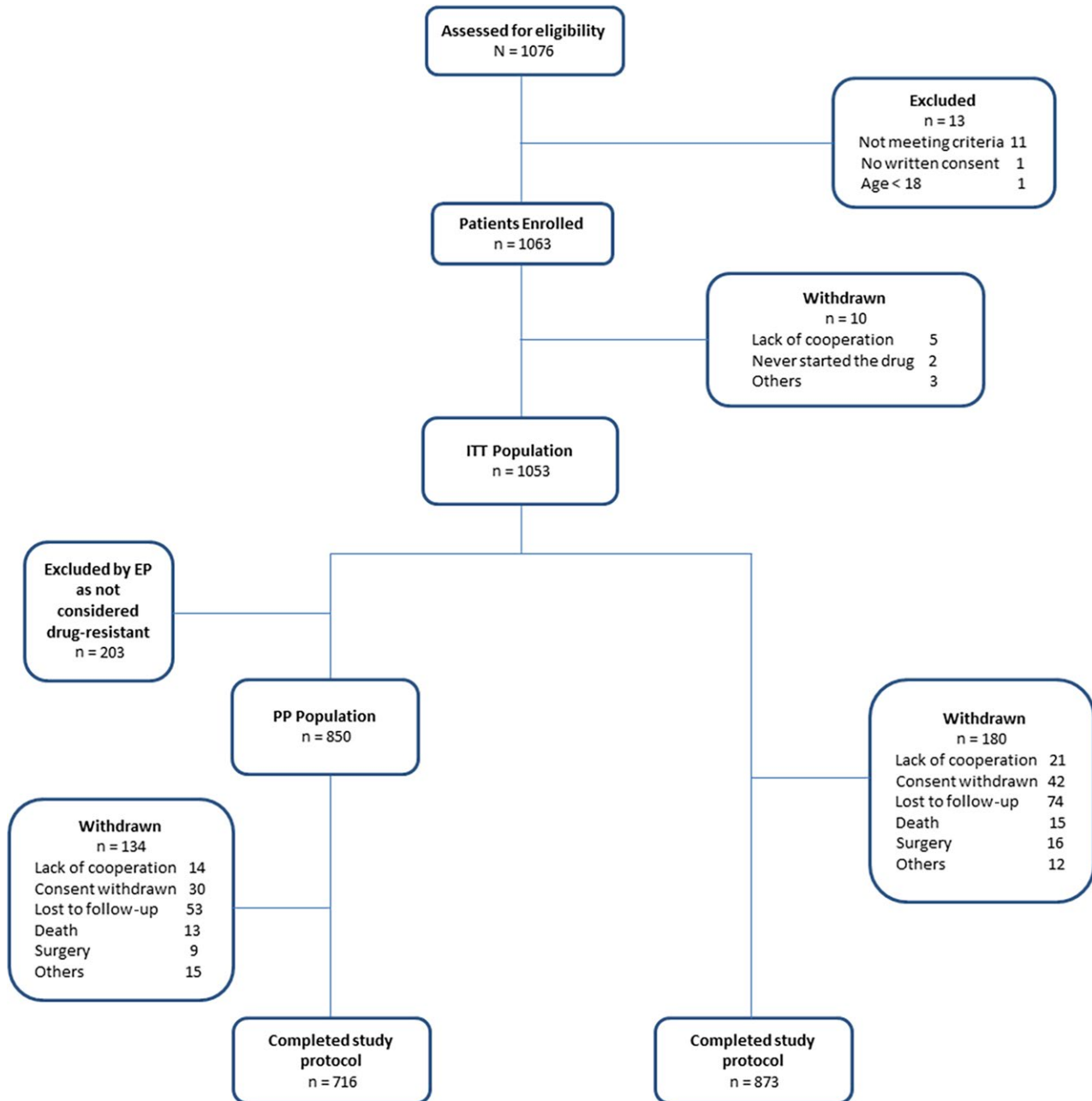
### 2.4 | Statistical analysis

According to the protocol, the primary analysis was conducted on the intention-to-treat (ITT) population, which included all patients considered to be drug-resistant by the enrolling physician and who had at least one subsequent clinical evaluation after baseline using the outcome category determined by the enrolling physician. A secondary analysis was done on the per-protocol (PP) population, which included all patients confirmed as drug-resistant by the EP and who had at least one subsequent clinical evaluation after baseline using the EP-validated outcome category. Frequency of outcome categories according to investigators and the EP were compared using the chi-square test.

## 3 | RESULTS

Of 1076 screened patients, 1063 were enrolled in the study and 1053 had at least one clinical assessment after baseline (ITT population). Of the 1053 patients, 203 (19.3%) were not considered drug-resistant by the EP and were instead considered to have “undetermined” treatment outcomes due to various reasons, including suboptimal use of previously tried AEDs or lack of adequate information. A resulting total of 850 patients were thus confirmed to be drug-resistant by the EP and had at least one postbaseline assessment (PP population; Figure 1). The ITT and PP populations were comparable in terms of clinical and demographic characteristics (Table 1).

Overall, the agreement between EP members was 96.3%, and the agreement between investigators and the EP was 70.4%. A detailed analysis, including reasons for disagreement, is reported in a separate publication.<sup>13</sup>



**FIGURE 1** Disposition of subjects. EP, expert panel; ITT, intention-to-treat; PP, per-protocol

As shown in Table 1, three of four patients in the ITT population had already discontinued at least two AEDs in the past, with the three most frequent reasons being lack of efficacy in 71.8% of cases, lack of efficacy and tolerability in 10.6%, and adverse effects in 9.8%. Three-quarters of patients (74.5%) were taking two or more AEDs at enrollment. The frequency distribution of AEDs prescribed in the past, continued at enrollment, and introduced at enrollment in the ITT population is shown in Figure 2. The three AEDs that were most frequently included in the treatment regimen at the time of enrollment were carbamazepine (37.6%), levetiracetam (LEV; 27.7%), and phenobarbital (26.0%), whereas the AEDs most frequently introduced at enrollment were

lacosamide (LCM; 41.4%), LEV (12.8%), and zonisamide (12.1%; Table 2).

A total of 17% of patients from the ITT population withdrew prematurely from the study as compared with 15.8% withdrawals from the PP population (Figure 1). In both populations, the most common reasons for withdrawal were lack of cooperation, withdrawal of consent, and loss to follow-up. Fifteen patients (1.4%) died during the study.

The response to the newly introduced AED, categorized according to ILAE criteria, is shown in Table 3. In the ITT population, 92 patients (8.7%) were considered by the investigators to have achieved seizure-free status, and 646 (61.3%) were considered treatment failures. Overall, seizure-free

**TABLE 1** Clinical and demographic data of the ITT and PP populations

|  | ITT, n = 1053      | PP, n = 850      |
|--|--------------------|------------------|
| Gender, male, n (%)                              | 504 (47.9%)        | 419 (49.3%)      |
| Age, y, median (range)                           | 43.4 (18.2-92.3)   | 42.9 (18.2-92.3) |
| Etiology, n (%) <sup>a</sup>                     |                    |                  |
| Unknown  | 485 (46.1%)        | 380 (44.7%)      |
| Structural                                       | 533 (50.6%)        | 440 (51.7%)      |
| Genetic  | 57 (5.4%)          | 49 (5.7%)        |
| Other; ie, metabolic, infectious, immune         | 5 (0.5%)           | 5 (0.6%)         |
| Age at onset, y, median (range)                  | 13 (0-86)          | 12 (0-86)        |
| Duration of epilepsy, y, median (range)          | 22 (0-68)          | 22 (0-68)        |
| Intellectual disability, n (%)                   | 234 (22.2%)        | 195 (22.9%)      |
| History of febrile seizures, n (%)               | 172 (16.3%)        | 144 (16.9%)      |
| History of status epilepticus, n (%)             | 92 (8.7%)          | 80 (9.4%)        |
| Seizures at baseline per 28 days, median (range) |                    |                  |
| Focal aware seizures                             | 4 (0.1-180)        | 5 (0.2-180)      |
| Focal impaired awareness seizures                | 4.0 (0.1-180)      | 1.5 (0.2-180)    |
| Focal to bilateral tonic-clonic seizures         | 1.0 (0.1-45)       | 1.6 1.5 (0.2-45) |
| AEDs taken at baseline, n (%)                    |                    |                  |
| Monotherapy                                      | <b>269 (25.6%)</b> | 182 (21.4%)      |
| Dual therapy                                     | 512 (48.6%)        | 424 (49.9%)      |
| 3 AEDs   | 214 (20.3%)        | 189 (22.2%)      |
| >3 AEDs  | 58 (5.5%)          | 55 (6.5%)        |
| Previously discontinued AEDs, n (%)              |                    |                  |
| 0  | 62 (5.9%)          | —                |
| 1  | 192 (18.2%)        | 166 (19.5%)      |
| 2  | 230 (21.8%)        | 180 (21.2%)      |
| 3  | 147 (14.0%)        | 129 (15.2%)      |
| 4  | 121 (11.5%)        | 107 (12.6%)      |
| 5  | 88 (8.3%)          | 75 (8.8%)        |
| 6  | 61 (5.8%)          | 57 (6.7%)        |
| >6   | 152 (14.4%)        | 136 (16%)        |

AED, antiepileptic drug; ITT, intention-to-treat; PP, per-protocol.

<sup>a</sup>Some patients are counted in more than one group.

status was achieved by 17.4% of patients for whom only two AEDs had previously failed, with the proportion of patients becoming seizure-free decreasing progressively with increasing number of previously failed AEDs (Figure 3A). Less than 2% of patients for whom more than six AEDs had failed achieved seizure-free status.

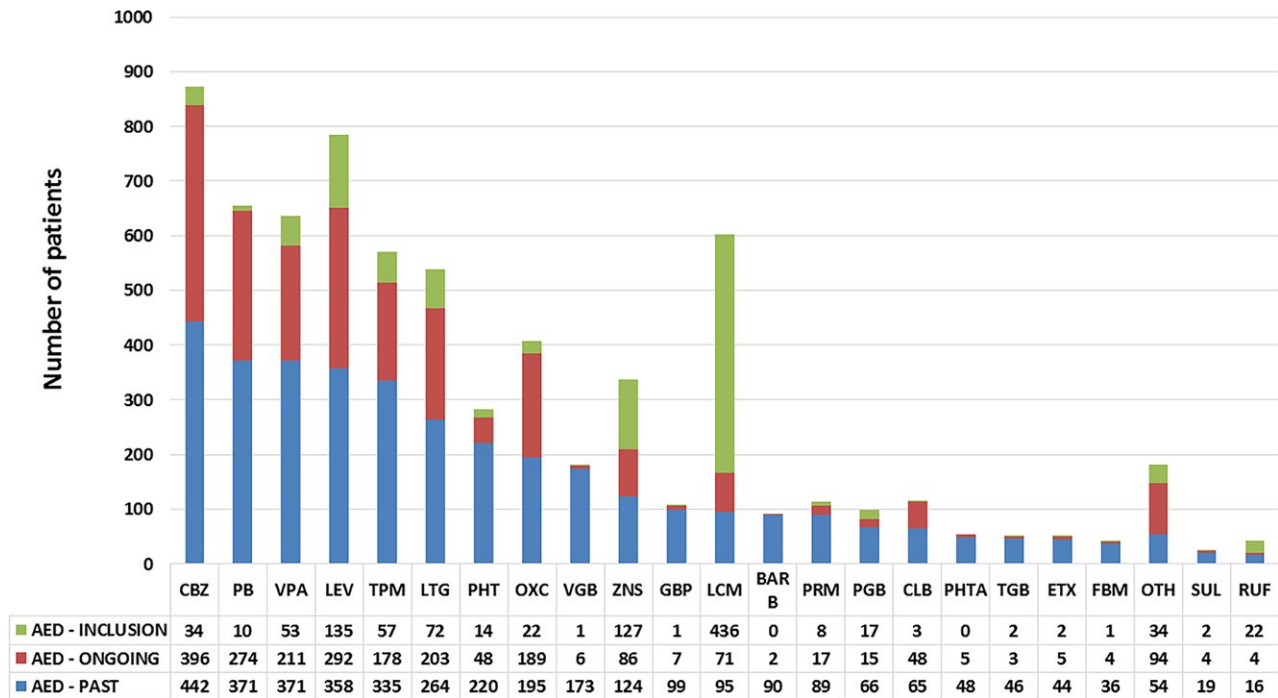
The proportion of patients achieving seizure freedom in the PP population was 7.6% based on the EP evaluation as compared with 8.3% based on the investigators' judgment (Table 3). In line with the disparity in assessments made at enrollment, the proportion of patients considered to have treatment failures was significantly higher in the investigators' assessments than in the EP assessments (62.9% vs 46.7%,  $\chi^2 = 53.5$ ,  $P < 0.0001$ ). Conversely, compared with the investigators' assessment, significantly more patients

were rated by the EP as having an undetermined outcome (Table 3). Overall, seizure-free status as related to the number of previously failed AEDs was lower in the PP population than in the ITT population (Figure 3B and 3C). Specifically, the proportion of patients achieving seizure-free status based on EP assessment was 11.8%, 8%, and 4.6% among patients for whom two, three, and four AEDs had failed, respectively, and <3% for patients for whom more than four AEDs had failed.

## 4 | DISCUSSION

This is the first study that, in addition to investigating outcome of treatment changes according to ILAE criteria,<sup>1</sup> provides





**FIGURE 2** Frequency and distribution of antiepileptic drugs (AEDs) in the intention-to-treat population. BARB, barboxalzone; CBZ, carbamazepine; CLB, clobazam; ETX, ethosuximide; FBM, felbamate; GBP, gabapentin; Inclusion, AEDs newly introduced at enrollment; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; Ongoing, AEDs present in the treatment regime at the time of enrollment; OTH, other (eg, clonazepam); OXC, oxcarbazepine; PAST, AEDs used in the past; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; PHTA, phenytoin association; PRM, primidone; RUF, rufinamide; SUL, sulthiame; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide

data validated by an independent EP. Agreement between expert pairs in applying ILAE criteria for categorization of treatment outcome was generally high, as reported in an earlier pilot study by other investigators. Agreement between investigators and the EP was very similar to that reported by a recent cross-sectional study that validated the ILAE definition in terms of reliability and validity.<sup>14</sup> Interestingly, the latter study also concluded that, for both reliability and validity, the ILAE definition compares favorably with previously proposed definitions of drug-resistant epilepsy.

Although in four of five cases the EP confirmed the diagnosis of drug-resistant epilepsy made by the investigator at enrollment, in one of five patients this diagnosis was not confirmed. These findings are in line with results from previous studies emphasizing the concept of “pseudo drug resistance,” meaning that a sizeable proportion of patients with uncontrolled seizures cannot be considered drug-resistant.<sup>15,16</sup> Inclusion of patients with pseudo drug resistance can also potentially explain discrepancies across studies in reported outcomes of treatment changes in patients considered to be drug-resistant.

Some authors have suggested that the ILAE definition of drug resistance may be overrestrictive,<sup>17–19</sup> and that seizure freedom rates after treatment changes in patients for whom two or more AEDs had failed can be substantial,

from about 20% to >50%.<sup>3,5,18–20</sup> However, those studies used different definitions of drug resistance, and treatment failures in the same studies may be different from the one resulting from a correct application of ILAE criteria. In our study, as many as 17.4% of patients who had been considered by the investigator as having experience failure with two AEDs achieved seizure freedom, but that proportion dropped to 11.8% when outcomes were reassessed by the EP and after excluding those cases where the diagnosis of drug-resistant epilepsy was not confirmed. Overall, our results may be regarded as supporting the validity of the ILAE definition of drug resistance and give clear figures on the probability of achieving seizure freedom with a newly introduced AED in adult patients who have been classified as having drug-resistant focal epilepsy, namely one in 10 after two AED failures and <3% after six or more failures. Our findings are in keeping with those reported by other authors, with the additional strength of being based on a large, externally validated population, evaluated prospectively and according to ILAE criteria. Interestingly, based on EP assessment, 45.6% of treatment outcomes were rated as undetermined at the end of follow-up. This was mainly attributed to failure to attain what the EP considered an adequate AED dose in the presence of persisting seizures, or to the decision to discontinue the drug before its potential

could be fully assessed. Therefore, we cannot exclude that some of these patients could have achieved seizure freedom at a higher dose, which would lead to our study underestimating the probability of achieving seizure freedom on a newly introduced AED. Although this limitation is acknowledged, in our observational setting a follow-up period of up to 34 months was not long enough to achieve seizure-free status in these patients.

The definition of seizure freedom is another element of novelty of our study. According to the ILAE definition, the effectiveness of a pharmacological intervention is

**TABLE 2** AED introduced at the time of enrollment (intention-to-treat population, n = 1053)

| AED           | n   |
|---------------|-----|
| Carbamazepine | 36  |
| Clobazam      | 34  |
| Clonazepam    | 3   |
| Ethosuximide  | 2   |
| Felbamate     | 1   |
| Gabapentin    | 1   |
| Lacosamide    | 436 |
| Lamotrigine   | 72  |
| Levetiracetam | 135 |
| Oxcarbazepine | 22  |
| Phenobarbital | 10  |
| Phenytoin     | 14  |
| Pregabalin    | 17  |
| Primidone     | 8   |
| Rufinamide    | 22  |
| Sulthiame     | 2   |
| Tiagabine     | 2   |
| Topiramate    | 57  |
| Valproic acid | 51  |
| Vigabatrin    | 1   |
| Zonisamide    | 127 |

AED, antiepileptic drug.

**TABLE 3** Response to the newly introduced antiepileptic drug according to International League Against Epilepsy criteria in the ITT and PP populations

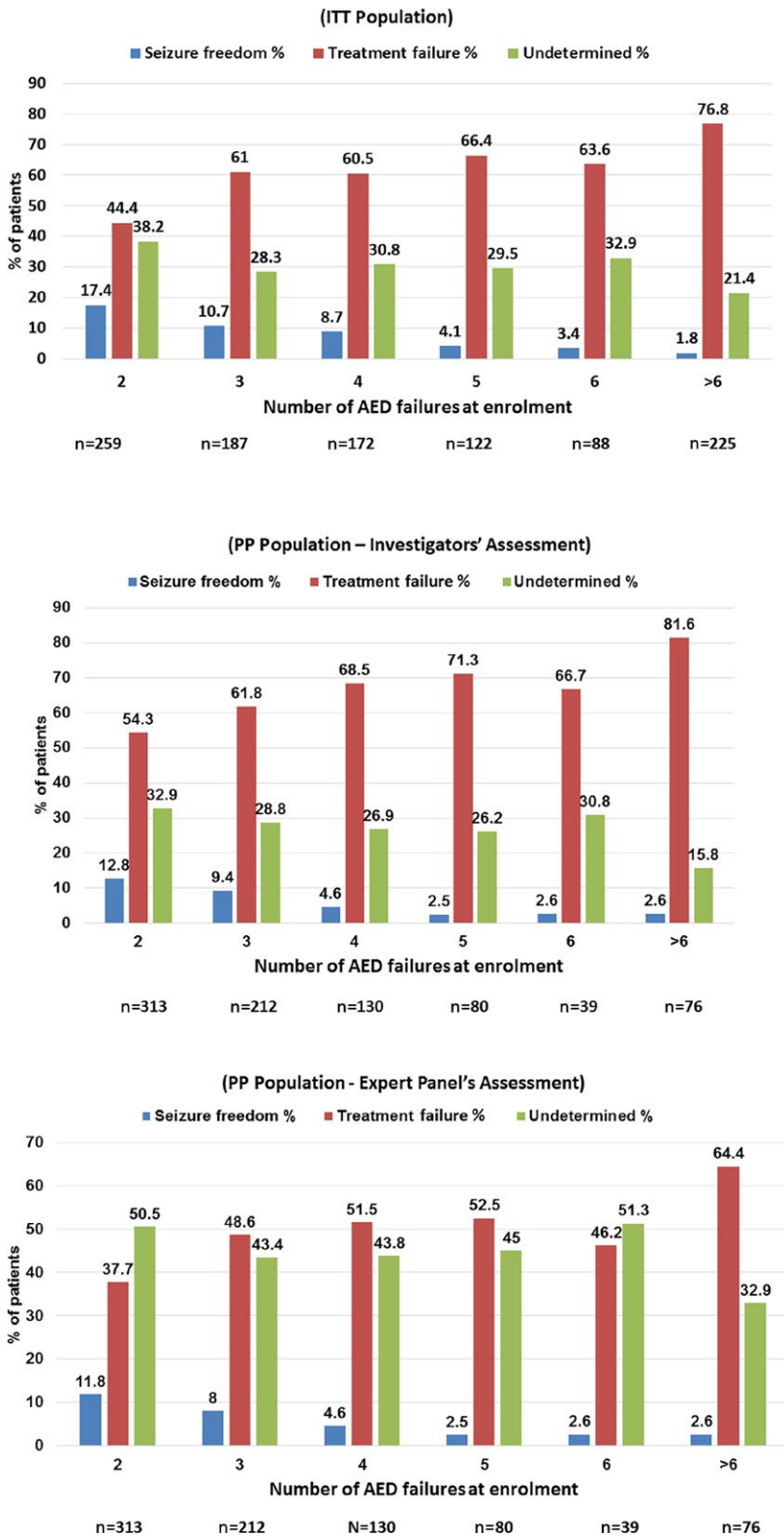
|                   | ITT population,<br>n = 1053  | PP population, n = 850    |                          |
|-------------------|------------------------------|---------------------------|--------------------------|
|                   | Investigators'<br>assessment | Investigators' assessment | EP assessment            |
| Seizure-free      | 92 (8.7%)                    | 71 (8.3%)                 | 65 (7.6%)                |
| Treatment failure | 646 (61.3%)                  | 535 (62.9%)               | 397 (46.7%) <sup>a</sup> |
| Undetermined      | 315 (29.9%)                  | 244 (27.7%)               | 388 (45.6%) <sup>a</sup> |

EP, expert panel; ITT, intention-to-treat; PP, per-protocol.

<sup>a</sup> $\chi^2 = 53.5$ ,  $df = 2$ ,  $P < 0.0001$  (investigators' assessment vs EP assessment in the PP population).

based on the longest interseizure interval in the 12 months preceding the drug trial. It is, therefore, evident that patients with infrequent seizures may need a period of >12 months without seizures to confirm that an individual patient responded to a specific drug trial. This point has important practical consequences: (1) it allows clinicians to inform patients in advance about the length of time that is needed to determine treatment response, and (2) it can guide further studies on the concepts of "relapse" and "sustained seizure freedom" in epilepsy. It is becoming clear that some patients with epilepsy present with a relapsing-remitting pattern as opposed to others having an unremittingly chronic time course. However, different authors seem to use different definitions of seizure freedom, and there has been considerable variation in the interseizure period required to classify a patient as having achieved seizure freedom. That some patients with drug-resistant epilepsy may subsequently go into remission (Figure 3) indicates that a diagnosis of drug resistance does not imply that seizures will persist for a lifetime,<sup>1,9</sup> but the ILAE definition will help in creating standardized criteria to identify specific prognostic categories.

Although our study has several strengths, it also has limitations. First, inclusion criteria were limited to adults with focal epilepsy to ensure a relatively homogeneous population, but this also implies that results may not necessarily be applicable to children or to patients with other types of epilepsy. Second, as discussed above, the probability of achieving seizure freedom on the newly introduced AED were probably underestimated, because a considerable proportion of patients had an undetermined outcome at the end of follow-up. Third, this was an observational study, and the choice of the newly introduced AED and dosing schedules were left to the clinical judgment of the individual investigator. For all these reasons, our study may be considered less informative than a randomized controlled trial. However, our study provides "real-life" outcome data with the advantage of being externally validated. Lastly, we recognize that a sizeable proportion of patients (about 40%) were started on LCM, and therefore outcomes are to some extent related to this drug.



**FIGURE 3** Treatment outcome in relationship to the number of previously failed antiepileptic drugs (AEDs). ITT, intention-to-treat; PP, per-protocol

This is explained by LCM having been introduced in Italy near the time of the study, subsequently introduced AEDs (perampanel, eslicarbazepine acetate, and brivaracetam) not yet being available at that time. Prescribing the newest option for patients for whom many other AEDs had already failed is

a common occurrence, known as the “latest drug phenomenon,” which seems to affect retention on treatment rather than seizure outcomes.<sup>21</sup>

In conclusion, this study demonstrates that in adults with an externally validated diagnosis of drug-resistant



focal epilepsy, seizure freedom rates achieved with a newly introduced AED were about 12% for patients who had previously experienced failure with two AEDs, becoming progressively less likely as the number of previously failed AEDs increased. These results may be regarded as supportive of the validity of the ILAE definition of drug resistance, provide clear validated figures regarding a patient's chances of becoming seizure-free on a new drug trial as a function of the number of previously failed AEDs, and underline the concept that drug resistance is not synonymous with medical intractability.

## ACKNOWLEDGMENTS

This study was sponsored by UCB Pharma. UCB Pharma was involved in the design and conduct of the study, and collection, management, and analysis of the data. The article was written entirely by the authors without external assistance. The authors received no remuneration for the preparation of the manuscript. UCB Pharma was offered a courtesy review of the manuscript, the comments on which were at the authors' discretion to address. The authors acknowledge Dr Antonio Colantoni as data manager. The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this study. The authors acknowledge Michaela Fuchs, PhD (Evidence Scientific Solutions, Horsham, UK) for assistance with journal formatting, which was funded by UCB Pharma, and Virginie Goffaux, DVM (UCB Pharma, Brussels, Belgium) for manuscript coordination.

## DISCLOSURE OF CONFLICT OF INTEREST

E.P. has received speaker fees or served as a consultant for Eisai, GW Pharma, Livanova, Medichem, Mylan, Sanofi, Sun Pharma, Takeda, and UCB Pharma, and has intellectual property rights with Wiley and Elsevier. M.M. has received consultancy fees from UCB Pharma, Eisai, Bial, and Elsevier and has intellectual property rights with Springer. B.F. is an employee of UCB Pharma. G.Z. has received speaker or consultancy fees from Eisai, Janssen-Cilag, Sanofi-Aventis, and UCB Pharma. O.M. has received speaker fees and research funding from UCB Pharma, Eisai, Sandoz, and Mylan. M.P.C. has received speaker fees, consultancy fees, and financial support for organizing courses and congresses from Sanofi, Novartis, Eisai, Livanova, UCB Pharma, and Somnomed. S.S. has received speaker and consultancy fees from Eisai and UCB Pharma. C.A.G. has received research grants from UCB Pharma, Eisai, and Bial, and speaker or consultancy fees from Bial, Eisai, and UCB Pharma. None of the other authors has any conflict of interest to disclose. We confirm that we have read

the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## COINVESTIGATORS

Carlo Andrea Galimberti (Pavia, principal investigator), Cristina Valisi (Pavia, site investigator); Francesco Paladin, Filippo Dainese (Venice, site investigators); Roberto Eleopra, Christian Lettieri, Giada Pauletto (Udine, site investigators); Tiziano Zanoni, Monica Ferlisi (Verona, site investigators); Francesco Pierini, Federica Ranzato (Vicenza, site investigators); Teresa Anna Cantisani, Chiara Piersanti, Federica Nardini, Michela Cecconi (Perugia, site investigators); Nicoletta Foschi, Chiara Fiori, Cristina Petrelli (Ancona, site investigators); Raffaele Rocchi, Lorenzo Celli, Daniela Marino (Siena, site investigator); Paolo Aloisi (L'Aquila, site investigator); Alfonso Iudice, Emanuele Bartolini (Pisa, site investigators); Marco Paganini, Anna Maria Romoli, Francesca Pizzo (Florence, site investigators); Gaetano Zaccara, Tramacere Luciana (Florence, site investigators); Angela La Neve, Teresa Francavilla, Marianna Ladogana (Bari, site investigators); Nicola Paciello (Potenza, site investigator); Giovanni Boero (Taranto, site investigator); Addolorata Mascia (Pozzilli, site investigator); Luigi Maria Specchio, Maria Grazia Pascarella (Foggia, site investigator); Anna Teresa Giallonardo, Jijnane Fattouch, Sara Casciato (Rome, site investigator); Oriano Mecarelli, Patrizia Pulitano, Alessia Zarabla (Rome, site investigator); Michele Feleppa, Maria Rosaria D'Argento (Benevento, site investigators); Francesco Habetswallner, Bernardo De Martino, Amelia Cutolo (Naples, site investigators); Maria Grazia Marciani, Andrea Romigi, Maria Albanese (Rome, site investigators); Salvatore Striano, Marta Ianniciello, Marianna De Vito, Luigi Del Gaudio (Naples, site investigators); Silvana Franceschetti, Davide Sebastiano Rossi (Milan, site investigators); Flavio Villani, Giuseppe Didato (Milan, site investigators); Fabio Minicucci, Emanuela Leopizzi (Milan, site investigator); Stefano Meletti, Laura Mirandola, Giada Giovannini (Modena, site investigators); Roberto Micheluzzi, Patrizia Riguzzi (Bologna, site investigators); Paolo Tinuper, Barbara Mostacci, Marcella Broli (Bologna, site investigators); Maria Paola Canevini, Giulia Scornavacca (Milan, site investigators); Gianpietro Sechi, Silia Fenu, Chiara Fois (Sassari, site investigators); Francesco Marrosu, Gianni Orofino (Cagliari, site investigators); Vito Sofia, Irene Pappalardo, Chiara Sueri, Loretta Giuliano (Catania, site investigators); Ornella Daniele, Leila Zummo (Palermo, site investigators); Francesco Pisani, Giuseppe Loddo, Cesare Stilo, Laura Rosa Pisani (Messina, site investigators); Umberto Aguglia, Cinzia Leonardi, Edoardo Ferlazzo, Marina Bellavia (Reggio Calabria, site investigators); Domenico Consoli, Caterina Gattuso (Vibo Valentia, site investigators); Maurizio Elia, Maria Grazia Figura (Troina, site

investigators); Gianadrea Ottonello, Daniela Arecco (Genoa, site investigators); Antonio Gambardella, Maria Pantusa (Catanzaro, site investigators); Fabrizio Monti, Marco Belluzzo, Marinella Tomaselli (Trieste, site investigators); Luigi Giuseppe Bongiovanni, Francesco Brigo (Verona, site investigators); Paola Banfi, Valeria Mariani (Varese, site investigators).

## ORCID

Marco Mula  <https://orcid.org/0000-0002-9415-3395>

## REFERENCES

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000;342(5):314–9.
2. Lhatoo SD, Sander JW, Shorvon SD. The dynamics of drug treatment in epilepsy: an observational study in an unselected population based cohort with newly diagnosed epilepsy followed up prospectively over 11–14 years. *J Neurol Neurosurg Psychiatry*. 2001;71(5):632–7.
3. Callaghan B, Schlesinger M, Rodemer W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia*. 2011;52(3):619–26.
4. Callaghan BC, Anand K, Hesdorffer D, et al. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol*. 2007;62(4):382–9.
5. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol*. 2007;62(4):375–81.
6. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. *Neurology*. 2008;70(1):54–65.
7. Alexandre V, Capovilla G, Fattore C, et al. Characteristics of a large population of patients with refractory epilepsy attending tertiary referral centers in Italy. *Epilepsia*. 2010;51:921–5.
8. Perucca E. Pharmacoresistance in epilepsy: how should it be defined. *CNS Drugs*. 1998;10(3):171–9.
9. Berg AT, Shinnar S, Levy SR, et al. Defining early seizure outcomes in pediatric epilepsy: the good, the bad and the in-between. *Epilepsy Res*. 2001;43(1):75–84.
10. Berg AT. Identification of pharmacoresistant epilepsy. *Neurol Clin*. 2009;27(4):1003–13.
11. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010;51(6):1069–77.
12. Bajacek M, Hovorka J, Nezadal T, et al. Is pseudo-intractability in population of patients with epilepsy still alive in the 21st century? Audit of 100 seizure-free patients, referred with the diagnosis of pharmacoresistant epilepsy. *Neuro Endocrinol Lett*. 2010;31(6):818–22.
13. Zaccara G, Mula M, Ferrò B, et al. Do neurologists agree in diagnosing drug resistance in adults with focal epilepsy? *Epilepsia*. 2019;60(1):175–83.
14. Téllez-Zenteno JF, Hernández-Ronquillo L, Buckley S, et al. A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. *Epilepsia*. 2014;55(6):829–34.
15. Carreño M, Aparicio J, Sierra A, et al. Are patients referred for presurgical evaluation drug resistant according to the new consensus definition? A study in a tertiary center. *Epilepsy Res*. 2012;98(2–3):277–80.
16. Hao X, Goldberg D, Kelly K, et al. Uncontrolled epilepsy is not necessarily the same as drug-resistant epilepsy: differences between populations with newly diagnosed epilepsy and chronic epilepsy. *Epilepsy Behav*. 2013;29(1):4–6.
17. Gomez-Alonso J, Gil-Nagel A. A graded system to categorize drug-resistant epilepsy. *Epilepsia*. 2010;51(11):2360–1.
18. Neligan A, Bell GS, Elsayed M, et al. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. *J Neurol Neurosurg Psychiatry*. 2012;83(8):810–3.
19. Ramos-Lizana J, Rodriguez-Lucenilla MI, Aguilera-López P, et al. A study of drug-resistant childhood epilepsy testing the new ILAE criteria. *Seizure*. 2012;21(4):266–72.
20. Berg AT, Levy SR, Testa FM, et al. Remission of epilepsy after two drug failures in children: a prospective study. *Ann Neurol*. 2009;65(5):510–9.
21. Mäkinen J, Peltola J, Raitanen J, et al. Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: the influence of age, gender, and the sequence in which drugs were introduced onto the market. *J Neurol*. 2017;264(7):1345–53.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Mula M, Zaccara G, Galimberti CA, et al. Validated outcome of treatment changes according to International League Against Epilepsy criteria in adults with drug-resistant focal epilepsy. *Epilepsia*. 2019;00:1–10. <https://doi.org/10.1111/epi.14685>