STUDY PROTOCOL: EFFICACY AND TOLERABILITY OF LOW VS. STANDARD DAILY DOSES OF ANTIEPILEPTIC DRUGS IN NEWLY DIAGNOSED, PREVIOUSLY UNTREATED EPILEPSY (STANDLOW). A MULTICENTER, RANDOMIZED, SINGLE-BLIND, PARALLEL GROUP TRIAL.

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List of abbreviations

AE = adverse events

AED =Antiepileptic drug

CRF = Case record form

DMC= Data monitoring committee

EEG = Electroencephalogram

FDA= Food and drug administration

GCP = Good clinical practice

GPL3 = General public license 3

ICH = International conference on harmonization

IEC = Independent ethics committee

ILAE= International League Against Epilepsy

IRB = Institutional review board

IRCCS = Istituto di Ricerca e Cura a Carattere Scientifico

NHS= National Health System

REB = Research ethics board

SAE= serious adverse events

SSL = Secure Sockets Layer

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1. Background and rationale

The efficacy of the first treatment in patients with newly diagnosed epilepsy is well-known. About 33-58% of patients achieve complete seizure remission with the first maintenance daily dose, defined as the dosage on which a patient is stabilized after the initial titration phase (Abimbola et al, 2011). However, with few exceptions, individual trials and Cochrane reviews show similar efficacy with differing maintenance dosages (Maguire et al, 2009). The initial maintenance dosage is rarely discussed in published reports, and the lack of specifically designed studies means that no consensus exists about what dosage should be used.

Twelve drugs have been marketed for use as monotherapy in Italy. The first standard maintenance dosages of these drugs reported in the Italian National Formulary (www.codifa.it) are the following: carbamazepine, 800-1600mg; phenobarbital, 100mg; phenytoin, 300mg; valproate, 1000mg; lamotrigine, 200mg; levetiracetam 1000mg; oxcarbazepine, 600mg; topiramate, 100-200mg; gabapentin, 900-3600mg; ethosuximide, 1000-1500mg; zonisamide, 300mg; lacosamide 200mg.

Published reports and common experience show that exposing patients to long-term treatment with higher dosages of antiepileptic drugs (AEDs) increases the risk of adverse effects and has a negative impact on quality of life (Gilliam, 2002). When AED treatment is given at low doses, adverse effects are no different from untreated individuals (Perucca et al, 2011). There are no published studies comparing low to standard doses of AEDs.

In 1996 the promoter started a nationwide randomized pragmatic trial comparing low to standard doses of carbamazepine, phenobarbital, phenytoin and valproate in children and adults with newly diagnosed epilepsy. Drug selection was left to the caring physician's judgment. 122 patients were randomized by 17 centers and followed for up to 36 months. 80 cases had complete and evaluable data. 73% of cases receiving low daily doses and 79% of those receiving standard doses entered 24-month remission. Compared to low doses, patients on standard doses had a higher chance of treatment change, mostly due to adverse events. In the last two years, the PI investigated the therapeutic habits of 26 italian epilepsy centers in terms of initial maintenance dose for each of the AEDs used as monotherapy in newly diagnosed patients. 19 of them replied, 12 opting for low doses and 7 for standard doses. The maintenance dose of each drug varied significantly as follows: carbamazepine, 400-1200; phenobarbital, 50-150; phenytoin, 150-400; valproate, 500-1500; lamotrigine, 50-400; levetiracetam 500-2000; oxcarbazepine, 450-1800; topiramate, 100-400; gabapentin, 600-3200; zonisamide, 100-400; lacosamide 100-200 mg.

On this background, our research hypothesis is that low doses of AEDs in adults with newly diagnosed previously untreated focal and focal-to-bilateral epilepsy are at least as effective as

standard doses but carry a significantly lower risk of adverse effects, are associated with a better quality of life and satisfaction, and translate into significant savings for the National Health System. The study can help define the lowest effective therapeutic strategy and, if possible, the lowest effective dose for each AED.

2. Study objectives

2.1. Primary objective

To demonstrate that the proportion of patients receiving a low dose of an AED and remaining seizure-free is not inferior to the proportion of patients who remain seizure-free after receiving a standard dose of the same drug.

2.2 Secondary objectives

To demonstrate that the proportion of patients experiencing intolerable drug-related adverse events is lower with a low than a standard dose.

To demonstrate that health-related quality of life (HRQOL) and satisfaction with treatment score higher with a low than a standard dose.

To demonstrate that, on a societal perspective, the treatment of newly diagnosed epilepsy with low AED doses will translate into savings in terms of contacts with the National Health System (in- and outpatient visits, drug expenditures).

2.3 Primary endpoint

The primary end-point is a treatment failure motivated by the need to change the assigned dose or the assigned drug for seizure relapse.

2.4 Secondary endpoints

Secondary endpoints include: 1. Treatment failure motivated by intolerable drug-related adverse events; 2. HRQOL total score at 12 months; 3. Patient's satisfaction at 12 months; 4. Total cost of health care resources consumed for the management of epilepsy during the first 12 months of the study.

3. Study design

This is a multicenter randomized pragmatic parallel-group single-blind non-inferiority trial. Italian epilepsy centers will participate in the study. Each center has been selected on the basis of high

standards in the management of epilepsy and on previous participation to studies coordinated by the PI.

3.1 Participating centers

The Promoter of the study is the Istituto di Ricerche Farmacologiche Mario Negri IRCCS.
The coordinating center for patients' enrolment is the ASST Monza Ospedale San Gerardo.
Satellite centers placed in the entire national territory will be involved in the study.

3.2 Inclusion criteria

Patients eligible for inclusion must satisfy all the following criteria:

1. Age 18 years or older;
2. Newly diagnosed previously untreated epilepsy, defined according to the ILAE definition (Fisher et al, 2014);
3. Having experienced focal and focal-to-bilateral seizures, defined according to the ILAE criteria (Commission, 1981);
4. Able to understand and comply with the study requirements and release a written informed consent.

3.3 Exclusion criteria

A patient will be excluded if at least one of the following criteria will be met:

1. Age less than 18 years;
2. Having experienced primarily generalized tonic and/or clonic seizures, or other (non-focal/focal-to-bilateral) seizure types;
3. Previous exposure to AEDs for a period > 7 days before randomization and a dose higher than the low dose of the study protocol
4. Requiring low or standard doses on account of individual needs;
5. Inability to understand the aims or modalities of the study;
6. Current pregnancy or planning to become pregnant during the study period (e.g. who are not post-menopausal, surgically sterile, or using inadequate birth control). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause;
7. Previous treatment with an antiepileptic drug;
8. Women unable to practice contraception for the duration of the treatment.
9. Poor compliance with assigned treatments;
10. Refusal to release written informed consent;

11. The study investigators will receive the summary of product characteristics (SPC) available for each study drug. Patients cannot be enrolled in the study if the contraindications/warnings described in the SPC are met.

3.4 Randomization

After informed consent, eligible patients will be randomized to receive a low or a standard dose of the assigned drug. Randomization will be centralized at the Istituto Mario Negri IRCCS, Milano. Randomization sequence will be created using SAS 9.4 (SAS Institute, Cary, NC, USA) statistical software and will be stratified by center with a 1:1 allocation using random block sizes of 4. Each center will receive randomization scratch-cards.

3.5 Data collection at baseline and during follow-up

The following variables will be collected at admission by the evaluating physician: date of birth, sex, height, weight, arterial blood pressure, heart rate, family history of epilepsy, history of febrile seizures, date of onset of seizures, seizure type(s), epilepsy syndrome or non-syndromic epilepsy, neurological and psychiatric examination (coded as normal or abnormal), first interictal EEG (coded as normal, slow or epileptiform), imaging findings (coded as normal or abnormal for seizure etiology), relevant comorbidities, concurrent treatments, HRQOL (using the Italian version of the QOLIE-31 inventory; Beghi et al, 2005), patient satisfaction (PSQ-18), laboratory examinations if available (CBC, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltranspeptidase, creatinine, alkaline phosphatase, calcium, phosphorus, sodium, potassium, ammonia, amylase). Each patient will be followed for 12 months. In the follow-up visits the same laboratory tests will be performed as per clinical practice or caring physician discretion, including the AED plasma concentration assay. Ad-hoc diaries will be given to each patient and/or caregiver for the collection of follow-up data. The diaries will include the number of seizures (with dates) and the type and severity of adverse events (with dates, outcome and actions). To preserve blindness, daily intake and timing of the assigned, but not the daily dose, will be recorded in the diaries. Any contact with the National Health System for the management of seizures and AEDs will be also noted in the diaries with dates. The contents of the diaries will be verified during each telephone contact by the evaluating physician and by the treating physician at the time of the face-to-face visits.

3.6 Baseline and follow-up visits

At the baseline visit (Visit 1), each patient with newly diagnosed epilepsy will be screened for eligibility. Patients satisfying all the selection criteria will be informed of the study aims and asked to release a written informed consent. All the baseline data will be collected in an electronic case report form (e-CRF) and the patient will be then randomized. Follow-up visits will be scheduled at the discretion of the caring physician but telephone contacts will be programmed at 4 weeks, 3, 6, 9 and a clinic on-site visit at 12 months. An interval of ± 1 week for the visit schedule is permitted. During each contact/visit the patient will be asked to report any seizure recurrence, adverse event and any additional information deemed important for the management of the disease. Patients will be invited to read the diaries and verify if any missing or incomplete information was present.

4. Study duration

Study duration: 36 months as indicated below:

- Administrative and ethical procedures: 6 months.
- Duration of patient enrolment: 12 months.
- Follow-up period: 12 months from the date of randomization.
- Database lock and statistical analysis: 30th-35th month.
- Final report and data publication: 36th month.
- Planned start of enrolment: as soon as the Ethics committee approval and signed contract are in house.

The end of study is considered the last patient last visit (LPLV).

5. Study population

Total number of patients: 374 considering 10% of expected dropouts.

Number of patients for each treatment arm = 168 (see Sample Size calculation for details).

6. Drug choice, tapering and maintenance daily dosages

The choice of the drug is left to the caring physician's discretion but it must be limited to the AEDs marketed for monotherapy use. All the study drugs will be used according to the respective SPCs, which will be sent by the promoter to all the study investigators.

For each individual drug, the following doses (in mg/day) have been selected as low vs. standard: carbamazepine, 300 vs 600; levetiracetam, 500 vs. 1000; valproate, 300 vs. 600; zonisamide, 150-300; oxcarbazepine, 600 vs. 1200; topiramate, 100 vs. 200; lamotrigine, 100 vs. 200; gabapentin, 450 vs. 900, lacosamide 100 vs. 200. Tapering to the assigned target dose will be performed as in

clinical practice but instructions will be imparted for each drug at the beginning of the study.

6.1 Treatment arms

1) *Low doses*
2) *Standard doses*

6.2 Concomitant Medications and Prohibited Treatments

Except for AEDs, there are no restrictions to the use of concomitant medications. For a correct outline of all drug interactions, the local investigator will be provided with the summary of product characteristics (SPC) of each individual AED used in the study. However, both subjects and investigators must keep records of all concomitant drugs on the concomitant medication page of the e-CRF along with daily dose and duration of use.

6.3 Patient numbering and treatment assignment

Eligible subjects will be enrolled and randomized during the same visit (Visit 1). At the end of this visit, if a subject fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log.

Patients will be identified by a unique subject number, which will be assigned by the site investigator consecutively. The subject number will determine the allocation of treatment. The treatment will be assigned through a central randomization. The assigned treatment will be recorded in the source documents as well as in the subject's e-CRF. Once assigned, a subject number will not be reused for another patient. For all participants, the subject number will not be changed during the entire study.

6.4 Treatment blinding

The study is single-blind. Only the evaluating physician will be blinded to the assigned treatment schedule.

6.5 Brand & generic drugs

For each product, the treating physician can use the brand or the generic formulation. However, physicians and patients will be allowed to shift from brand to a generic formulation (where available) and vice versa and from one generic formulation to another during the study period.

6.6 Need to change the study drug or add another compound and premature withdrawal

An unscheduled phone contact will also take place soon after a relapse: the patients will also be instructed to call a member of the study staff within 24 h after an ictal event. If the study staff is confident about the epileptic nature of the event, the treating physician may decide to modify the treatment schedule; the patient will be thus instructed to change the AED doses or the treatment and come for the final visit within 72 hours. Otherwise, the patient will be invited to come for a clinic visit within the next 72 hours.

6.7 Study drugs dispensation

This is a not-for-profit study, according to Health Ministry Decree 17.12.2004. The same decree certifies that study drug costs are covered by the national health service (Art 2) in case of not-for-profit studies and if the study drug is used as per marketing authorization.

In this study, the drugs will be dispensed by the hospital pharmacies. When the patient receives the information on the drug and the daily dose assigned by randomization, he/she (or the treating physician) will contact the center's pharmacist to obtain the assigned drug. The drug will be reimbursed according to the directives imparted by each Italian region (eg, File F). Drugs will be labeled by pharmacists according to Vol 4 GMP, Annex 13, Labelling. All used (empty) and unused drug will be returned in the provided packaging to the investigator's staff for drug accountability. After being verified by the Clinical Monitor, all unused drug will be destroyed at the centre.

7. Visit schedule and assessments (see Study Flow Chart)

The recruitment period will last for 12 months and enrolled patients will be followed for 12 months after randomization. Enrolled patients will undergo periodic visits with a predetermined schedule:

7.1 Baseline evaluation.

The following assessments will be accomplished:

a. Verification of all inclusion and exclusion criteria
b. Recording of demographic data and clinical parameters: date of birth, sex, height, weight, arterial blood pressure and heart rate.
c. Physical, neurological and psychiatric examination
d. General clinical history: concomitant diseases and medications
e. Assessment of birth control methods for women in childbearing age
f. Family history of epilepsy, history of febrile seizures, date of onset, type of seizures, seizure

frequency at onset, epileptic syndrome or non-syndromic epilepsy

g. Administration of the QOLIE-31 and PSQ-18 inventories
h. Results of first interictal EEG
i. Results of available blood sample withdrawal
j. Imaging findings (MRI or CT scan as per clinical indication)
k. Randomization and assignment of allocated treatment
l. Delivery of seizure diary
m. Appointment for the next visit at the discretion of the caring physician. First telephone contact at 4 weeks.

7.2 Follow-up visits.

Follow-up visits will be scheduled at the discretion of the caring physician but telephone contacts will be programmed at 4 weeks, 3, 6, 9 and an on-site clinic visit at 12 months. An interval of ± 1 week for the visit schedule is permitted. During each contact the patient will be asked to report any seizure recurrence, adverse event and any additional information deemed important for the management of the disease. Patients will be invited to read the diaries and verify if any missing or incomplete information was present.

The following evaluations will be performed during site visits:

1. Evaluation of possible relapses, compliance with treatment schedule and adverse events;
2. Recording of clinical parameters: weight, arterial blood pressure, heart rate;
3. Neurological examination;
4. General clinical history: concomitant diseases and medications;
5. Recording of the plasma concentration of the assigned drug and laboratory examinations previously specified (only if required as per clinical practice);
6. Administration of the QOLIE-31 and PSQ-18 inventories (only at 12 months);
7. Report of a standard, interictal EEG if performed as per clinical practice;
8. Report of the daily intake of assigned drug and timing of the assigned dose;
9. Report of all the contacts with the National Health System (NHS) for the management of seizures and AEDs;
10. Receipt of the seizure diary, control for quality and completeness, and delivery of a new diary.

The diaries will be examined by an investigator different from the treating physician (the evaluating physician) who will be blinded to the assigned drug schedule

The following evaluations will be performed during phone contacts:

1. Evaluation of possible relapses, compliance with treatment schedule and adverse events;
2. General clinical history: concomitant diseases and medications;
3. Report of the daily intake and timing of the assigned dose;
4. Report of a standard, interictal EEG, if performed;
5. Recording of the plasma concentration of the assigned drug and laboratory examinations previously specified, if performed;
6. Report of all the contacts with the NHS for the management of seizures and AEDs.

In case of seizure relapse or treatment change due to adverse events, the patient will exit the study and antiepileptic treatment will be modified if required by the treating physician.

7.3 End of study visit

The final visit will be a clinic visit, scheduled at 12 months (± 1 week) after randomization; the following assessments will be performed:

1. Evaluation of possible relapses, compliance with treatment schedule and adverse events;
2. Recording of clinical parameters: weight, arterial blood pressure, heart rate;
3. Neurological examination;
4. General clinical history: concomitant diseases and medications;
5. Assessment of birth control methods for women in childbearing age
6. Recording of the plasma concentration of the assigned drug (only if required as per clinical practice);
7. Report of a standard, interictal EEG if performed as per clinical practice;
8. Administration of the QOLIE-31 and PSQ-18 inventories;
9. Receipt of the seizure diary and control for quality and completeness.

The patient will exit the study and antiepileptic treatment will be continued or modified in case of seizure relapse or changed due to adverse events, if required by the local investigator.

7.4 Treatments Medication Compliance

Subjects will be instructed to use the study medication in compliance with the treatment schedule. If

the subject is compliant with the schedule and no seizures are reported, he/she will be advised to come to the Centre for the next visit or to be contacted by phone; otherwise, he/she will exit the study and the final visit will be performed within 72 hours. The treating physician will be responsible for the assessment of subject's compliance with study medication at each visit. Compliance will be measured counting the weekly amount of assigned drug. Poor compliance will be defined by taking less than 75% of assigned dose and/or absence of druk intake for 2+ consecutive days. This information will be recorded and retained in the subject's record.

Subjects will be instructed to return all drug consumed (empty) and unused, as well as a completed diary, at the end of study visit and during each visit at discretion of the physician before end of study visit. Reconciliation of drug consumed and drug remaining will be logged on the drug dispensing and return log, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. The investigator will be responsible for the assessment of subject compliance with study medication at each visit and the count of returned study medication. This information will be recorded and retained in the subject's record.

7.5 Physical examination, weight, height

The patient will undergo a complete physical examination, including the measurement of height and weight.

7.6 Vital signs

Vital signs (systolic and diastolic blood pressure and heart rate) will be measured at each site visit by the treating physician or a designated person.

7.7 Scales and e-CRF

The QOLIE-31 inventory will be used at the baseline and last visit to measure HRQOL (Annex QOLIE-31). The Patient Satisfaction Questionnaire will be used at the baseline and last visit to measure patient's satisfaction (Annex PSQ-18).

The e-CRF used for the collection of demographic and clinical data is appended (Annex Case Report Form).

7.8 Subject Diary

Each subject will receive a diary in which he/she must record all seizure relapses (Annex Patient's diary). Any adverse events (AEs) occurring between one visit and the next, any new concomitant therapy, and any change in previously started study or concomitant therapies will be captured in the

diary.

7.9 Birth control method

All females of childbearing potential will declare, at randomization visit, to use highly effective birth control methods according to the recommendations related to contraception and pregnancy testing in clinical trials (1.combined (estrogen and progesteron) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); 2. progesteron-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); 3. intrauterine device (IUD); 4. intrauterine hormone-releasing system (IUS); 5. bilateral tubal occlusion; 6. vasectomised partner; 7. sexual abstinence). All females of childbearing potential will perform a pregnancy test at randomization visit and at the end of study visit.

During the following visits, a confirmation of birth control method will be asked. Patients who become pregnant during the study will be withdrawn.

In post-menopause women, a postmenopausal state is defined as absence of menses for 12 months without an alternative medical cause.

8. Safety

Safety monitoring for all patients enrolled in the study will performed as done in clinical practice. Monitoring includes safety assessments and clinical evaluation, as scheduled in the flow chart. All AEs and serious adverse events (SAEs) will be recorded. Patient's diaries about AEs and/or concomitant medication will not be copied but will be considered source documents. AE documentation by the investigator will include the date of onset and duration, as well as the severity and causality of each AE, and the actions taken, including the discontinuation of the experimental drug, where required.

8.1 Adverse events

The Investigator is responsible for recording all AEs observed during the study.

Definition of AE: An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of SAE: A SAE is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Medically significant events, which do not meet any of the criteria above, but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above.

Medical and scientific judgment should be exercised in deciding whether an event is "serious" in accordance with these criteria.

Hospital admissions and/or surgical operations planned before the study are not considered AEs if The illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Adverse reaction: All untoward and unintended responses to an investigational medicinal product related to any dose administered.

The definition covers also medication errors and uses outside of what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

An Adverse Drug Reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose.

An Unexpected Adverse Drug Reaction is defined as any adverse reaction, the nature of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'.

8.2 Severity

The severity of the AE will be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the subject's daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject's usual daily activity.

Seriousness: The judgment as to whether the event is serious is usually made by the reporting investigator who must conform to the standard definition.

The physician will assess the seriousness, intensity, and causality of each AE, and the actions taken, including the discontinuation of the experimental drug, where required by the site investigator or the patient (Refer to GCP/1997 and to D.L N 211/2003 for explanation about how and when to refer to AE, SAE, SUSAR, DAR and their definitions).

8.3 Causality

The causal relationship between the study drug and the AE will be characterized as unrelated, unlikely, possible, probable or unknown (unable to judge). Events can be classified as "unrelated" if there is not a reasonable possibility that the study medication caused the AE.

- An "unlikely" relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression, or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.

- A "possible" relationship suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.

- A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g. because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

The assessment of whether there is a reasonable possibility of a causal relationship is made by the investigator. In the absence of information on causality from the reporting investigator, the Istituto di Ricerche Farmacologiche Mario Negri IRCCS should consult the reporting investigator and encourage him/her to express an opinion on this aspect. The causality assessment given by the investigator should not be downgraded by the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. If the Istituto di Ricerche Farmacologiche Mario Negri IRCCS disagrees with the investigator's causality assessment, the opinion of both the investigator and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS should be provided with the report.

For more detail about seriousness criteria, refer to "Common Terminology Criteria for Adverse Events (CTCAE)" Version 5.0 Published: Nov 27, 2017 from the U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute.

8.4 AE Reporting

All AEs, regardless of severity and whether or not they occurred during the treatment or follow-up period, are to be recorded on the appropriate AE pages in the CRF. The investigator will include the date of onset and duration of the AE, as well as the severity and causality of each AE, and the actions taken. Each event should be recorded separately.

The investigator shall report all AEs and SAEs into the e-CRF, without reporting to Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

8.5 Reporting of SAEs and SUSARs

Any SAEs will be reported immediately to Istituto di Ricerche Farmacologiche Mario Negri IRCCS pharmacovigilance representative within 24 hours of the investigator becoming aware of the event. The SAE form, along with any additional information necessary in evaluating the SAE (such as laboratory reports or hospital notes), should be included. The Istituto di Ricerche Farmacologiche Mario Negri IRCCS will keep detailed records of all AEs related to the study that are reported by the investigator.

The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by their unique code numbers.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031) and subsequent amendments define the following terms:

A suspected unexpected serious adverse reaction (SUSAR) that is fatal or life-threatening must be

reported to the competent authority and ethics committee within 7 days after the Istituto di Ricerche Farmacologiche Mario Negri IRCCS became aware of the event. Any additional information must be reported within 8 days of sending the first report.

A SUSAR that is not fatal or life-threatening must be reported to the competent authority and ethics committee as soon as possible (within 15 days) after the Istituto di Ricerche Farmacologiche Mario Negri IRCCS becomes aware of the event.

8.6 Follow up of AE/SAE/DAR/DAE/SUSAR

Any AE/SAE/DAR/DAE/SUSAR observed from screening/randomization up to the end of the study will be followed up to resolution. Resolution means that the subject has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE.

8.7 Data Monitoring Committee (DMC)

According to the EMEA GUIDELINE ON DATA MONITORING COMMITTEES (January 2006) a Data Monitoring Committee (DMC) is an external group of independent experts assessing the progress, safety data and efficacy endpoints of this clinical study. In order to do so, a DMC may review study information (on a patient level or treatment group level) during the conduct of the study. Based on its review, the DMC provides the Principal Investigator with recommendations regarding study modification, continuation or termination. Safety monitoring will be the major task for a DMC. The DMC might need access to efficacy information to perform a risk/benefit assessment in order to weigh possible safety disadvantages against a possible gain in efficacy.

Based on the results of the monitoring activities, the DMC is expected to consider recommendations about stopping the trial for efficacy and/or safety and/or for sample size adjustment without violating the concepts behind the original study protocol.

If changes in the study conduct are recommended by a DMC, sufficient information should be provided to allow the Principal Investigator to decide whether and how to implement these recommendations. The implementation of any DMC recommendation is solely the responsibility of the Principal Investigator who is also free to neglect (in whole or in part) recommendations of a DMC.

The DMC has to be fully functional before enrolment into the study starts to enable it to respond to any safety signal.

As DMC work is a multidisciplinary task, the DMC needs expertise from different scientific areas. The member of the DMC will include a biostatistician, a member of an ethical committee, a neurologist and a pharmacovigilance expert.

All members of the DMC will be qualified persons, they should also have practical experience with conducting clinical trials, a good understanding of the problems and limitations of clinical trials, have no financial interest in the outcome of the study.
The DMC will meet after the enrollment of at least 25% of patients and after three months of study. The following DMC meeting will take place after the enrollment of 50% of patients.

9. Resource utilization

The study foresees a charge for the hosting institutions. The randomization (Visit 1) and follow-up visits as well as drug delivery will be performed by local investigators who have completed adequate training and are listed in the signature log. This trial is an independent investigation according to the Ministry Decree (DM) # 43 dated December 17 2004. In keeping with the Italian law, the trial will receive an insurance coverage (DM 213, July 14 2009). Laboratory tests will be performed by the local laboratory and prescribed as part of the routine evaluation.

10 Data review and management

10.1 Site monitoring

On site monitoring will be performed in order to review the -CRFs for completeness and accuracy and will instruct site personnel to make any required corrections or additions. Where needed, remote monitoring will be performed.

10.2 Data collection

All trial demographic and clinical data will be collected by the designated investigators at each scheduled visit. The CRFs are made accessible to the Istituto di Ricerche Farmacologiche Mario Negri IRCCS or by the study site investigators, one copy being retained at the study site.

10.3 Database management and quality control

A web-based Clinical Data Management System (CDMS/eCRF), named FEATHER, is provided by Istituto di Ricerche Farmacologiche Mario Negri IRCCS to capture and verify study data.
Each eCRF user will be authorized to access to the application only through a protected computer (client) and providing personal credentials to login.
eCRF manager/administrator organizes users in different roles groups (es. project manager, data manager, clinical monitor, study investigators). Some groups will be able to edit and store patient's data and other groups will validate and lock the inserted data.

Every enabled user would be authorized to view/edit only datas necessary to complete his task.
Locked data can't by modified.
eCRF activity is automatically logged and data editing is stored in a digital audit trail. eCRF captured data is stored and protected in hight-security network.

10.4 Outcome measures, statistical methods and data analysis

Expected outcomes are the following:

1. compared to patients assigned to standard daily doses, patients receiving low daily doses of AEDs are expected to incur in similar rates of seizure recurrence;
2. compared to patients assigned to standard daily doses, patients receiving low daily doses of AEDs are expected to undergo significantly less treatment changes due intolerable drug-related adverse events;
3. compared to patients assigned to standard daily doses, patients receiving low daily doses of AEDs are expected to experience less drug-related intolerable adverse events;
4. compared to patients assigned to standard daily doses, patients receiving low daily doses of AEDs are expected to experience a better quality of life;
5. the National Health System is expected to incur in significant savings with low daily doses of AEDs.

Primary outcome

The proportion of patients experiencing a treatment failure motivated by the need to change the assigned dose or the assigned drug for seizure relapse during the follow-up.

Secondary outcomes

1. the proportion of patients experiencing a treatment failure motivated by intolerable drug-related adverse events during the follow-up;

2. QOLIE-31 total score at the last visit;

3. the score of the seven PSQ-18 subscales (general satisfaction, technical quality, interpersonal manner, communication, financial aspects, time spent with doctor, accessibility and convenience) at the last visit;

4. the mean daily patient’s cost of health care resources consumed for the management of epilepsy during the first 12 months of the study.

Descriptive statistics will be provided for all the data collected at admission, comparing the two

treatment regimens. Numerical variables will be described using means, standard deviations, medians and ranges, while categorical variables using frequencies and percentages. The proportion of patients experiencing the primary end-point over the entire follow-up will be estimated using Kaplan-Meier survival curves. The difference between the two treatment arms in the proportion of patients experiencing the primary endpoint, with 95% confidence intervals (95% CI), will be calculated at 1, 3, 6, 9 and 12 months, and compared to the non-inferiority margin (m). In presence of variables at admission having a different distribution in the two treatment groups and that could have an effect on treatment response (possible confounders), a multivariable analysis will be also performed using a Cox's proportional hazards model, adjusted for these variables. A hazard ratio (HR), with the corresponding 95% CI, will be reported, and compared to a relative risk (RR) obtained considering as reference the proportion of patients experiencing the primary endpoint in the standard dose arm (p_0) and taking into account the non-inferiority margin (RR=(p_0+m)/p_0).

The secondary end-point will be evaluated using Kaplan-Meier survival curves, comparing the two treatment arms with the log-rank test. In presence of possible confounders with a different distribution in the two treatment arms at baseline, a Cox's proportional hazards model will be used.

The QOLIE-31 total score, the seven PSQ-18 subscales scores at the last visit, and mean daily patient's costs will be compared, separately, between treatment arms using the t-test, the Wilcoxon-Mann-Whitney test, or a multivariable linear regression model.

Subgroup analyses will be performed separately for sex, age groups, drug, seizure types (focal/focal-to-bilateral), etiology (known/unknown), and center.

10.5 Interim-analysis

After enrolment of 100 patients, an interim-analysis will be performed with the following purposes: 1. To verify the relapse rate in the two treatment arms and stop the trial if more relapses have occurred in the low dose arm; 2. To check the relapse rate and re-do the power calculations if the rate significantly differs from that used to calculate the sample size when planning the study.

10.6 Sample size calculation

The sample size is based on the primary efficacy end-point. The non-inferiority margin is a relative 20% difference, as stipulated by the ILAE, up to a maximum of an absolute 15% difference between the two dosing schedules for the primary endpoint. Assuming a one-sided p of 0.025 and that the proportion of patients who will not have a seizure in the low dose and standard dose groups is 60%, 168 patients per group provides 80% power to test whether a low AED dose is non-inferior

to a standard dose. Assuming 10% drop-out rate, the required sample size will be 374 patients.

11 Administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the purposed informed consent must be reviewed and approved by a properly constituted IRB/IEC/REB before study start.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to monitors.

11.3 Informed consent form and Informed consent procedures

Eligible patients may be included in the study after proving written IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient.

11.4 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment.

Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval in according to the Italian legislation. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol.

In according with the GCP rules and the Italian legislation, the acceptance of an amendment of the study protocol by each participating institution is subjected to the local IRB/IEC/REB approval.

11.5 Insurance

In keeping with the Italian law, the trial will receive an insurance coverage (DM 213, July 14 2009).

11.6 Publication of study results

The results of the study will be published whether or not the experimental treatment is considered superior to standard treatment.

12. References

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Study flow-chart.

Activities	**V1-baseline**	**TC 4 weeks (±1 week)**	**TC 3 months (±1 week)**	**TC 6 months (±1 week)**	**TC 9 months (±1 week)**	**V12 END OF STUDY 12 months (±1 week)**	**On site visit at discretion of the physician before end of study visit**	**On site visit at discretion of the physician before end of study visit**	**On site visit at discretion of the physician before end of study visit**	**On site visit at discretion of the physician before end of study visit**
Informed consent signature	X									
Inclusion criteria	X									
Exclusion criteria	X	X	X	X	X	X	X	X	X	X
Vital signs	X					X	X	X	X	X
Physical examination	X					X				
Neurological examination	X					X	X	X	X	X
Psychiatric examination	X									
Concomitant diseases	X	X	X	X	X	X	X	X	X	X
Concomitant treatments	X	X	X	X	X	X	X	X	X	X
Birth control	X	X	X	X	X	X	X	X	X	X
Epilepsy history	X									

QOLIE 31 and PSQ-18 inventories	X					X				
First interictal EEG	X									
Results of follow-up interictal EEG (if performed)		X	X	X	X	X	X	X	X	X
Imaging (CT, MRI) findings	X									
AED plasma concentration and other biochemical/hematological parameters (if performed)	X	X	X	X	X	X	X	X	X	X
Randomization	X									
Assessment of seizures, AE/SAE		X	X	X	X	X	X	X	X	X
Assessment of contacts with the NHS		X	X	X	X	X	X	X	X	X
Delivery of patient's diary	X									
Assessment of patient's diary data		X	X	X	X	X	X	X	X	X
Return of patient's diary						X				
Assessment of compliance		X	X	X	X	X	X	X	X	X

Next contact/visit schedule	X	X	X	X	X		X	X	X	X
Final questions						X				

*Visit at 4 weeks, 3, 6 and 9 months will be performed by phone (TC). The other visits will be performed as clinic on-site visits.

PROTOCOL APPROVAL PAGE Version 3.0 December, 20 2021

Ettore Beghi MD **Date**

Istituto di Ricerche Farmacologiche Mario Negri IRCCS

Milano, Italy

I have read the Protocol Final Version 3.0 Dec, 20 2021. I agree to conduct this study as outlined herein.

Investigator Name

Investigator Institution

Investigator Signature **Date**