PART 1: Administrative Details	
Full Study Title	A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Basket Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Patients with Anti-N-Methyl-D-Aspartic Acid Receptor (NMDAR) or Anti-Leucine-Rich Glioma-Inactivated 1 (LGI1) Encephalitis.
Protocol/ Document Number	Revised Version 3.0 dated 25th August 2022
Date of Receipt of the Application	20th December 2022
Phase of Study	3
Study Registration Details	**PACTR202308468197623** Clinical trial approval certificate no. **FDA/CT/242**
Name and Address of Applicant(s)	Professor Fred Stephen Sarfo Department of Medicine, Komfo Anokye Teaching Hospital (KATH)
Name and Address of Sponsor(s)	F. Hoffman – La Roche / Chugai Pharma Co. Ltd Grenzacherstrasse 124 4070 Basel Switzerland
Name and Address of Principal Investigator(s)	Professor Fred Stephen Sarfo Principal Investigator Department of Medicine Komfo Anokye Teaching Hospital (KATH) P. O. Box 1934, Kumasi Tel.: +233243448464
Study Sites	Department of Medicine, Komfo Anokye Teaching Hospital (KATH)
Study Duration	5 years 5 months
FAPAR Number	FDA/CT/PAR/242

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	Satralizumab : Below 40kg: 60mg or matching placebo 40-100kg: 120mg or matching placebo Above: 180mg or matching placebo
Justification of Investigational Product(s) including comparators	The rationale meets an unmet need as there is no treatment for the management of encephalitis. However, participants will be randomized to receive Satralizumab or matching placebo in combination with any of the underlisted background therapy: 1. Mabthera 100mg & 500mg concentrate for solution for infusion 2. Mabthera 1400 & 1600 mg solution for subcutaneous injection 3. Methylprednisolone 40 mg powder for solution for injection 4. Mycophenolate Mofetil 500mg Film-Coated Tablets 5. Prednisolone 5mg Tablets 6. Cyclophosphamide Injection 500mg 7. Azathioprine 50mg Tablets The use of placebo in this setting helps to establish the efficacy and safety of satralizumab in clinical situations that represent the real-world scenario for patients with Autoimmune Encephalitis (AIE).

PART 3: Study Summary

Study Objectives

Primary Objective: To evaluate the efficacy of Satralizumab compared with placebo on degree of disability and clinical severity.

Secondary objective:

1. To evaluate the efficacy of Satralizumab compared with placebo
2. To evaluate the safety of Satralizumab compared with placebo

Exploratory Objective:

To evaluate the durability of response to satralizumab compared with placebo

Study Design

This Phase III, randomized, double-blind, placebo-controlled, multicenter study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo for the treatment of NMDAR encephalitis and LGI1 encephalitis. For efficacy analyses, the N=methyl-D-aspartic acid receptor (NMDAR) AIE and anti-

PART 3: Study Summary

leucine-rich glioma-inactivated 1 (LGI1) AIE cohorts will be treated as separate populations in a basket study design. The study will include a screening period of up to 28 days, during which patients' eligibility will be evaluated for study participation. Screening will be followed by:

• Part 1: a primary treatment period of 52 weeks

• Part 2: an optional extension period lasting approximately 2 years from when the last participant enters the extension period or until commercial satralizumab is available for the treatment of AIE.

A pharmacokinetic (PK) interim analysis will be performed once approximately 30 participants across both cohorts (to include approximately 15 participants receiving satralizumab) have received a minimum of 8 weeks of study treatment, to confirm that target concentrations are achieved.

The study will be conducted at approximately 75 sites in 12−15 countries, including, but not limited to, North America, Europe, Latin America, and Asia. Approximately 102 participants in the NMDAR AIE cohort and 50 participants in the LGI1 AIE cohort will be enrolled across all sites in a global enrolment phase. If at least 1 participant is enrolled in the China sites during the global enrolment phase, then after completion of the global enrolment phase additional participants may be enrolled in an extended China enrolment phase at China's sites including mainland China, Hong Kong, and Taiwan. The global population will include all participants enrolled during the global enrolment phase (including participants enrolled at China's sites during that phase), and the China subpopulation will include all participants enrolled at China's sites (i.e., during both the global enrolment phase and the extended China enrolment phase).

Eligibility Criteria

Inclusion criteria

1. Capable of giving signed informed consent.
2. Reasonable exclusion of tumor or malignancy before baseline visit (randomization) The screening guidelines for detection of thymoma, teratoma, and malignancy should be followed.
3. Onset of AIE symptoms 9 months before randomization
4. Has received their first acute first-line therapy more than 6 weeks prior to randomization (baseline visit).

Exclusion criteria list

Participants are excluded from the study if any of the following criteria apply:

1. Any untreated teratoma or thymoma at baseline visit (randomization) Teratoma or thymoma detected prior to or during the screening period is allowed if deemed cured after treatment (usually surgical removal) by 1 week prior to baseline
2. History of carcinoma or malignancy, unless deemed cured by adequate treatment with no evidence of recurrence for 5 years before screening (except basal cell and squamous

PART 3: Study Summary

cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured)

3. For patients with NMDAR AIE, history of negative anti-NMDAR antibody in CSF using a cell-based assay within 9 months of symptom onset
4. Historically known positivity to an intracellular antigen with high cancer association (e.g., anti-Hu, anti-Ma2, anti-CRMP5, anti-Yo, anti-amphiphysin, AMPA, mGluR5, and GABAB) or GAD-65
5. Historically known positivity to any cell surface neuronal antibodies other than NMDAR and LGI1 (e.g., caspr2, IgLON5, DPPX, GABAA, and neurexin-3α)
6. Confirmed paraneoplastic encephalitis
7. Confirmed central or peripheral nervous system demyelinating disease (e.g., multiple sclerosis, chronic inflammatory demyelinating polyneuropathy)
8. Alternative causes of associated symptoms, including CNS infections, septic encephalopathy, metabolic encephalopathy, epileptic disorders, mitochondrial disease, Klein-Levin syndrome, Creutzfeldt-Jakob disease, rheumatologic disorders, Reyes syndrome, or inborn errors of metabolism
9. History of herpes simplex virus encephalitis in the previous 24 weeks
10. Any previous/concurrent treatment with IL-6 inhibitory therapy (e.g., tocilizumab), alemtuzumab, total body irradiation, or bone marrow transplantation
11. Any previous treatment with anti-CD19 antibody, complement inhibitors, neonatal Fc receptor antagonists, anti−B-lymphocyte stimulator monoclonal antibody (e.g., belimumab)
12. Any previous treatment with T-cell depleting therapies, cladribine, or mitoxantrone
13. Treatment with oral cyclophosphamide within 1 year prior to baseline
14. Treatment with any investigational drug (including bortezomib) within 24 weeks prior to screening (or within 5 half-lives of the investigational drug; whichever is longer)
15. Concurrent use of more than one IST (e.g. azathioprine, mycophenolate mofetil, or IV cyclophosphamide) as background therapy. The combination of an OCS with another permitted IST drug is allowed.
16. Contraindication to all of the following rescue treatments: rituximab, IVIG, high-dose corticosteroids, or IV cyclophosphamide

Sex of participants
Male and Female

Age boundaries
Adolescents and Adults aged >12 years with definite or probable NMDAR encephalitis and Adults aged > 18years with LGI1 encephalitis.

Date of Commencement (Expected or Actual)

PART 3: Study Summary

1st March 2024 (Expected)

Status of Study:

Status of commencement not yet communicated.

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The quality of the Investigational product Satralizumab has been assessed by the FDA. The applicant submitted the following documents which were reviewed and found satisfactory to fulfill the quality requirement of the trial:

1. GMP Certificates from

- Catalent Pharma Solutions, LLC, 10381 Decatur Road, Philadelphia, Pennsylvania (PA) 19154, United States (USA)
- Genentech, Inc, 1 DNA Way, South San Francisco, California (CA) 94080, United States (USA)
- Charles River Laboratories, Inc., 466 Devon Park Drive, Wayne, Pennsylvania (PA) 19087, United States (USA
- Bioreliance Limited, Todd Campus, West of Scotland Science Park, Glasgow, G20 0XA, UK
- Chugai Pharma Manufacturing Co., 16-3, Kiyohara-Kogyo danchi, Utsunomiya-city, Tochigi, Japan
- DHL Solutions Fashion GmbH, In der Au 9, Florstadt, Hessen, 61197, Germany
- F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4058, Basel

2. WN43174 Investigational Medicinal Product Dossier for Satralizumab, Prefilled Syringe, 60mg/0.5 mL
3. WN43174 Investigational Medicinal Product Dossier for Satralizumab, Prefilled Syringe, 120mg/1 mL
4. WN43174 IMPD for Satralizumab 120mg/1ml & Satralizumab 60mg/0.5ml – Safety & Efficacy

Safety

The hypothetical clinical safety risks from the subcutaneous injection of visible particles are immunogenicity, hypersensitivities (including anaphylactic reactions) and injections site reactions. Safety of satralizumab 120 mg/mL prefilled syringes drug product was confirmed in patients with NMOSD in the open-label extension period of both Phase III studies (BN40898 and BN40900), as demonstrated by the absence of anaphylaxis, serious hypersensitivity reaction/injection related reactions and granuloma

PART 4: Scientific Discussion

The following documents were reviewed for the safety requirement of the trial:

- Investigator's Brochure version 13 dated 29th April 2022 for Enspryng (Satralizumab).
- WN43174 Investigational Medicinal Product Dossier for Satralizumab, Prefilled Syringe, 60mg/0.5 mL
- WN43174 Investigational Medicinal Product Dossier for Satralizumab, Prefilled Syringe, 120mg/1 mL
- WN43174 IMPD for Satralizumab 120mg/1ml & Satralizumab 60mg/0.5ml – Safety & Efficacy

Primary Safety Endpoints

1. Incidence of treatment-emergent adverse events (TEAEs).
2. Change from Baseline in laboratory assessments (complete blood count, chemistry, and coagulation).

Secondary Safety Endpoints:

1. Incidence, seriousness, and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
2. Change from baseline in targeted vital signs, clinical laboratory test results, ECG results, weight, height (< 18 years only), and C-SSRS

Efficacy

Satralizumab disposition was characterized in a total of four studies including healthy volunteers (Study SA-001JP; single-ascending dose [SAD]), RA patients (Study SA-105JP; multiple-ascending dose [MAD]), and patients with NMOSD in the two Phase III trials (Studies BN40898 and BN40900).

WN43174 IMPD for Satralizumab 120mg/1ml & Satralizumab 60mg/0.5ml – Safety & Efficacy was reviewed for the underlisted efficacy requirement of the trial.

Primary Efficacy Endpoint

The proportion of participants with modified Ranking Scale (mRS) score improved ≥ 1 from baseline and no use of rescue therapy at Week 24.

Secondary Efficacy Endpoints:

Time to mRS score improvement ≥ 1 from baseline without use of rescue therapy
• Time to rescue therapy
• Time to seizure freedom (seizure freedom defined as a cessation of seizures for at least 6 consecutive weeks) or cessation of status epilepticus without use of rescue therapy
• Change in CASE score from baseline at Week 24
• MOCA total score at Week 24
• RAVLT score at Week 24 (LGI1 AIE cohort)
• mRS score at Week 24 (as measured on a 7-point scale; NMDAR AIE cohort)

PART 4: Scientific Discussion

However the FDA noted that the use of the mRs scale as a primary endpoint does not adequately capture the efficacy in the core symptoms of acute encephalitis. Based on the scientific advice from European Medicines Agency, it is recommended that the CASE score is used as a co-primary endpoint. Applicant was asked to review the endpoints for this study and this was satisfactorily provided.

Overall comments

After initial review, the application was deferred with queries to be addressed by the applicant. Following the satisfactory response to all queries on the submission, the study was approved and issued a clinical trial certificate.

The applicant is committed to ensuring that the study is conducted in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

All participants will consent to the protocol prior to participation in any study-related activity.

Based on the assessment of medical and ethical principles, the anticipated benefits to the participant justify the foreseeable risks and inconveniences related to the conduct study.

PART 5: Application Review Process

The application was reviewed under the routine approval pathway with a decision taken in 46 working days

PART 6: Status after Review

The study was approved on 13th February 2024. Applicant to request for approval from the FDA as per section 5.7.1 of FDAs Guideline for Good Clinical Practice prior to shipment of Investigational Products.

References:

1. Investigational Medicinal Product Dossier for Satralizumab, prefilled syringe, 60 mg/0.5 mL.

2. Investigational Medicinal Product Dossier for Satralizumab, prefilled syringe,120 mg/0.5 mL.

3. Protocol Revised Version 3.0 dated 25th August 2022

4. Investigator's Brochure Version 14 dated April 2023 for Enspryng (Satralizumab).

5. FDA's Clinical Trial Assessment form version for Clinical Trial Application version 1.0 dated 2nd September 2019.

6. FDA's Clinical Trial Assessment form version for Quality Trial Application version 1.0 dated 2nd September 2019.

7. The Concept of Benefit / Risk. Presentation to the APEC Preliminary Workshop on Review of Drug Development in Clinical Trials by Celia Lourenco.

8. ICH E6(R2) guideline for good clinical practice dated 9 November 2016.

9. ICH E2A guideline for clinical safety data management: definitions and standards for expedited reporting dated 27 October 1994.

10. ICH E8 general considerations for clinical trials dated 17 July 1997

11. ICH E9 statistical principles for clinical trials dated 05 February 1998

12. ICH E10 choice of control and related issues in clinical trials dated 20 July 2000

13. ICH E17 general principles for planning and design of multi-regional clinical trials