CIELO: A randomized, double-blind, placebo-controlled, Phase 3 basket study of satralizumab in patients with NMDAR- or LGI1-antibody encephalitis

Jeffrey M. Gelfand[1], Hesham Abboud[2], Sarosh R. Irani[3], Hideto Nakajima[4], Amanda Piquet[5], Sean J. Pittock[6], E. Ann Yeh[7], James Overell[8], Sharmila Rajan[9], Muna El-Khairi[10], Soon-Tae Lee[11]

[1]UCSF Weill Institute for Neurosciences, Department of Neurology, San Francisco, CA, USA; [2]Case Western Reserve University, UH Cleveland Medical Center, Cleveland, OH, USA; [3]Nuffield Department of Clinical Neurosciences, University of Oxford, UK; [4]Nihon University, Division of Neurology, Department of Medicine, Tokyo, Japan; [5]University of Colorado Health Neurosciences Center, Anschutz Medical Campus, CO, USA; [6]Center for Multiple Sclerosis and Autoimmune Neurology, Mayo Clinic, Rochester, MN, USA; [7]The Hospital for Sick Children (SickKids), University of Toronto, Canada; [8]F.Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Genentech, Inc.,San Francisco, CA, USA; [10]Roche Products Ltd., Hertfordshire, UK [11]Seoul National University Hospital, Seoul, South Korea

INTRODUCTION and OBJECTIVE

- Autoimmune encephalitis (AIE) is a group of rare, severe, antibody-mediated neurological diseases characterized by prominent neuropsychiatric symptoms[1,2]
- The most common subtypes of AIE are those with antibodies targeting the N-methyl-D-aspartic acid receptor (NMDAR) or leucine-rich glioma-inactivated 1 (LGI1)[2]
- There are currently no approved treatments for AIE, and evidence-based treatments that reduce long-term cognitive and physical disability, as well as persistent seizures and disabling symptomology are needed[3,4]
- People with AIE have elevated levels of the multifunctional cytokine interleukin-6 (IL-6)[5]
- Processes regulated by IL-6 signaling, such as B- and T-cell differentiation, B-cell proliferation, survival and functioning of autoantibody producing plasma cells, and blood−brain barrier regulation, are thought to have a role in AIE pathogenesis[5–9]
- Anecdotal reports of IL-6 receptor (IL-6R) inhibition in AIE have described clinical benefits; hence IL-6R is a therapeutic target of interest[10]
- Satralizumab is a humanized, monoclonal recycling antibody that targets the soluble and membrane-bound forms of the IL-6R, blocking IL-6 signaling[11]
- CIELO (NCT05503264) is the first study of satralizumab in patients with AIE, evaluating the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of satralizumab compared with placebo

METHODS

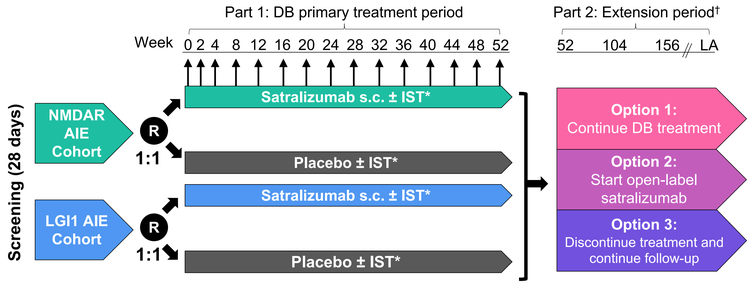
- CIELO will enroll ~102 patients aged ≥12 years with a diagnosis of probable or definite NMDAR AIE and ~50 patients aged ≥18 years with LGI1 AIE who have:
  - Onset of AIE symptoms ≤9 months prior to randomization
  - Modified Rankin Scale (mRS) score ≥2 at randomization
- Patients will be stratified as “new onset” or “incomplete responder” (**Table 1**)

Table 1. Definitions of "New onset" and “Incomplete responder" for inclusion criteria

	New onset	Incomplete responder
Acute first-line therapy	≤6 weeks before randomization	>6 weeks before randomization
Prior treatment	No immunotherapy additional to acute first-line therapy	Treatment with other immunotherapy in addition to acute first-line therapy*

*RTX initiated ≥2 months before screening (last dose ≥4 weeks before randomization), IST treatment ≥2 months before screening. OCS, or repeated pulse therapy; patients should have no improvement in mRS score within 4 weeks before randomization with prior immunotherapy, and patients who have received repeated courses of acute first-line therapy must have completed treatment ≥2 weeks before randomization. IST, immunosuppressive therapy; mRS, modified Rankin Scale; OCS, oral corticosteroids; RTX, rituximab.

Figure 1. CIELO study design summary



- CIELO (**Figure 1**) includes a 52-week double-blind primary treatment period (Part 1), followed by an optional extension period (Part 2)
- In Part 2, patients can either continue double-blind treatment, receive open-label satralizumab, or discontinue treatment and continue follow-up assessments

↟Treatment administered. *Incomplete responders may continue to receive the following background IST treatments: AZA, MMF, and intravenous cyclophosphamide. Patients may receive baseline OCS, which must be tapered from Week 4. All patients are permitted to receive symptomatic AIE medications. †The extension period lasts ~2 years from when the last patient enters the extension period. AIE, autoimmune encephalitis; AZA, azathioprine; DB, double-blind; IST, immunosuppressive therapy; IV, intravenous; LA, last administration; LGI1, leucine-rich glioma-inactivated 1; MMF, mycophenolate mofetil; NMDAR, N-methyl-D-aspartic acid receptor; OCS, oral corticosteroids; PK IA, pharmacokinetic interim analysis; R, randomized; s.c., subcutaneous.

Primary endpoint

- Proportion of patients with a mRS score improvement ≥1 from baseline without the use of rescue therapy at Week 24

Rescue therapy is defined as initiation or increase in dose of immunosuppressive therapy, rituximab, oral corticosteroids (OCS), the use of repeat first-line immunotherapy, or failure to taper OCS according to the protocol due to worsening or lack of improvement in AIE

Secondary endpoints

Not in hierarchical order, and will be tailored to the individual cohort

- Time to mRS score improvement ≥1 from baseline without use of rescue therapy
- Time to rescue therapy
- Time to seizure freedom or cessation of status epilepticus without use of rescue therapy
- Change in Clinical Assessment Scale of Encephalitis (CASE) score from baseline at Week 24
- Montreal Cognitive Assessment (MOCA) total score at Week 24
- Rey Auditory Verbal Learning Test (RAVLT) score for LGI1 AIE cohort at Week 24
- mRS score for NMDAR AIE cohort at Week 24, as measured on a 7-point scale

Safety

- Incidence, seriousness, and severity of adverse events
- Change from baseline in targeted vital signs, electrocardiogram results, clinical laboratory test results, weight, and height (<18 years only)

PK/PD

- Serum IL-6 and soluble IL-6R levels
- Serum and/or cerebrospinal fluid concentrations of satralizumab

Exploratory endpoints

- Degree of disability, clinical severity, mood, quality of life, and functional living
- Additional exploratory biomarker assessments including longitudinal assessments

CONCLUSIONS

- Randomized evidence to guide treatment decisions is urgently required in AIE
- CIELO will assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of IL-6 inhibition with satralizumab in patients with NMDAR AIE and LGI1 AIE
- CIELO will recruit at approximately 83 sites across 15 countries, with 17 sites in the USA
- To find recruiting sites near you, scan the below QR code

REFERENCES

1. Graus F, et al. *Lancet Neurol* 2016;15:391–404; **2.** Dalmau J and Graus F. *N Eng J Med* 2018;378:840–51; **3.** Abboud H, et al. *J Neurol Neurosurg Psychiatry* 2021;92:757–768; **4.** Trewin BP, et al. *Curr Opin Neurol* 2022;35:399–414; **5.** Ciano-Petersen NL, et al. *Brain Comm* 2022;4: fcac196; **6.** Lehmann-Horn K, et al. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e669; **7.** Kishimoto T, et al. In: Nakao K, et al (eds). Innovative Medicine: Basic Research and Development. Tokyo: *Springer* 2015, 131–147. DOI:10.1007/978-4-431-55651-0_11; **8.** Bien CG, et al. *Brain* 2012;135:1622–1638; **9.** Sun B, et al. *Nat Rev Neurol* 2020;16:481–492; **10.** Lee W-J, et al. *Neurotherapeutics* 2016;13:824–832; **11.** Yamamura T, et al. *N Eng J Med* 2019;381:2114–2124.

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