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ADISINSIGHT REPORT

Lazertinib: First Approval

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Abstract
Lazertinib (LECLAZA®) is an oral, third-generation, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) being developed by Yuhan and Janssen Biotech for the treatment of non-small cell lung cancer (NSCLC). It is a brain-penetrant, irreversible EGFR-TKI that targets the T790M mutation and activating EGFR mutations Ex19del and L858R, while sparing wild type-EGFR. In January 2021, lazertinib received its first approval for the treatment of patients with *EGFR* T790M mutation-positive locally advanced or metastatic NSCLC who have previously received EGFR-TKI therapy. This article summarizes the milestones in the development of lazertinib leading to this first approval.

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Lazertinib (LECLAZA®): Key Points

An oral EGFR-TKI being developed by Yuhan and Janssen Biotech for the treatment of NSCLC

Received its first approval on 18 January 2021 in the Republic of Korea

Approved for the treatment of patients with *EGFR* T790M mutation-positive locally advanced or metastatic NSCLC who have previously received EGFR-TKI therapy

1 Introduction

Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) have been the standard of care for patients with non-small cell lung cancer (NSCLC) harbouring *EGFR* activating mutations [e.g. exon 19 deletions (Ex19del) or exon 21 L858R point mutation] [1–3]. However, most patients receiving EGFR-TKIs eventually develop resistance to first-generation (gefitinib, erlotinib) or second-generation (afatinib, dacomitinib) drugs. The primary mechanism of acquired resistance to these drugs is an *EGFR* exon 20 point mutation leading to a threonine to methionine substitution at amino acid position 790 (T790M) [1, 2]. This led to the development of third-generation TKIs, which specifically target the *EGFR* T790M mutation.

Lazertinib (LECLAZA®) is an oral, third-generation, EGFR-TKI being developed by Yuhan and Janssen Biotech for the treatment of NSCLC. It is a brain-penetrant, irreversible EGFR-TKI that targets the *EGFR* T790M mutation and the activating *EGFR* mutations Ex19del and L858R, while sparing wild type-EGFR. On 18 January 2021 [4], lazertinib received its first approval for the treatment of patients with *EGFR* T790M mutation-positive locally advanced or metastatic NSCLC who have previously received EGFR-TKI therapy [5]. The recommended dosage of lazertinib is 240 mg once daily taken orally at the same time every day without regard to food. *EGFR* T790M mutation status must be evaluated prior to treatment using an in vitro diagnostic medical device approved by the Ministry of Food and Safety of South Korea. Treatment should be continued until disease progression or unacceptable toxicity. If dose reduction of lazertinib is needed, dosage should be reduced to 160 mg once daily [5].

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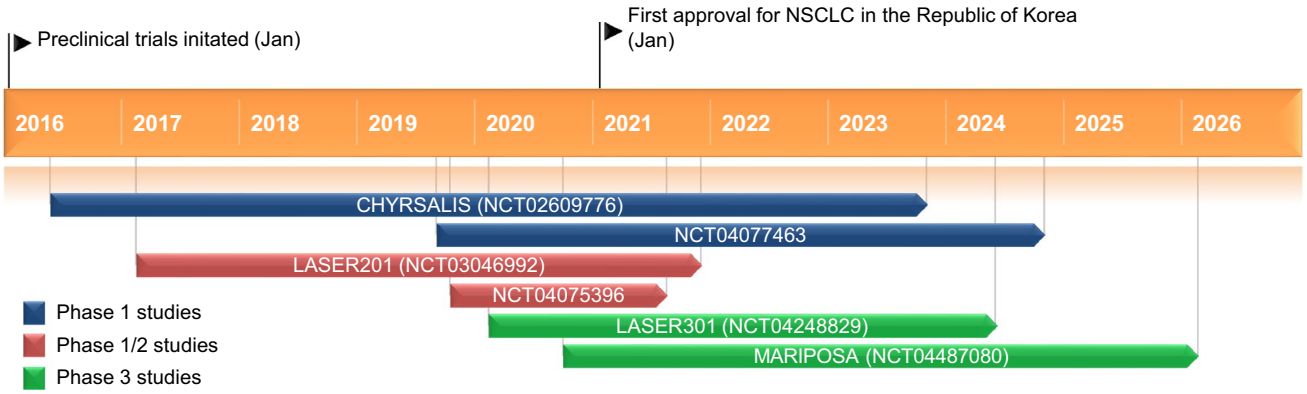


Key milestones in the development of lazertinib for the treatment of non-small cell lung cancer

1.1 Company Agreements

In July 2015, Genosco and Yuhan Corporation entered into a collaboration for the development and commercialization of lazertinib (formerly YH25448 and GNS-1480), for the treatment of NSCLC [6]. In November 2018, Yuhan entered into a licensing and collaboration agreement with Janssen Biotech, Inc. to develop Lazertinib for the treatment of patients with NSCLC. As part of the agreement, Janssen will assume responsibility for development, manufacturing and commercialization with exclusive worldwide rights to Lazertinib excluding the Republic of Korea, where the rights are retained by Yuhan. [7].

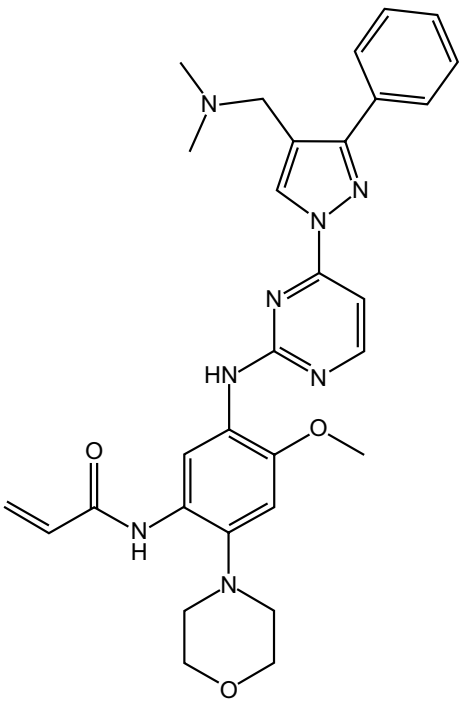
2 Scientific Summary

2.1 Pharmacodynamics

Lazertinib is a mutant-selective EGFR inhibitor with high selectivity (half maximal inhibitory concentrations of 1.7–20.6 nmol/L) for *EGFR* single (Ex19del, L858R, T790M) and double (Ex19del/T790M and L858R/T790M) mutations [5, 8]. Lazertinib was more selective and at least as potent as osimertinib in in vitro studies; on the other hand, lazertinib exhibited less activity against wild type *EGFR* than osimertinib. Lazertinib inhibited EGFR downstream signalling pathways, including phosphorylation of EGFR, AKT and ERK, in lung cancer cell lines bearing *EGFR* activating and T790M mutations. It induced apoptosis in *EGFR*-mutant lung cancer cell lines, as indicated by an increase in cleaved Bim-EL protein and activated caspase 3/7 activation [5, 8].

Lazertinib was significantly ($p < 0.05$) more effective than equimolar concentrations of osimertinib in inducing tumour regression in an *EGFR*-mutated mouse brain metastasis model [8]. It showed high blood-brain permeability as indicated by intracranial tumour/plasma and intracranial tumour/brain area under the concentration–time curve (AUC) ratios of 7.0 and 7.9, respectively. Lazertinib demonstrated potent antitumour activity in a patient-derived xenograft model of *EGFR*-mutant NSCLC and in a patient with NSCLC harbouring *EGFR* T790M mutation [8].

Mechanisms of resistance to lazertinib were generally similar to those reported in patients treated with other third generation EGFR-TKIs, although there were differences in frequencies [9]. In the pivotal, phase 1/2 study LASER201 (NCT03046992) in patients with advanced *EGFR*-mutated NSCLC, the most common resistance mechanisms to



Chemical structure of lazertinib

lazertinib were *EGFR* T790M loss ($n = 21$) and *PIK3CA* alterations ($n = 5$). Next-generation sequencing (NGS) of 74 genes was performed on paired plasma circulating tumour DNA (ctDNA) collected from 47 patients at screening and progressive disease. ctDNA was detected at baseline in all 47 patients and in 43 of 45 patients at progression. At baseline, an *EGFR* activating mutation was detected in 85% (40/47) of patients (38 of whom had disease progression and were included in the mechanism of resistance analysis) and *EGFR* T790M was detected in 68% (32/47) of patients. Of the 38 patients included in the analysis, *EGFR* T790M was detected in 31 (nine patients at screening and disease progression, 21 patients at screening only and one patient at progressive disease only) and 'on-target' mechanisms of resistance were detected in seven (18%) patients, including *EGFR* C797S ($n = 3$; all in cis with T790M), *EGFR* amplification ($n = 3$) and *EGFR* T854A ($n = 1$). 'Off-target' mechanisms of resistance were seen in 34% (13/38) of patients, including *PIK3CA* ($n = 5$), *MET* amplification ($n = 4$), *ERBB2* ($n = 2$), *KRAS* ($n = 1$) and *BRAF* ($n = 1$) [9].

2.2 Pharmacokinetics

The pharmacokinetics of lazertinib have been assessed in healthy subjects and in patients with NSCLC [5]. After single- or multiple-dose administration, the peak plasma concentration of lazertinib increased in a dose proportional manner over a dose range of 20–320 mg, while the area under the plasma concentration-time curve increased in a slightly greater than dose proportional manner [10]. Across all dose levels, the median time to peak plasma concentration of lazertinib was reached 2–4 hours after single- or multiple-dose administration [5, 10]. Steady state was reached by day 15 and the mean accumulation ratio was 2–3 after 22 days of dosing [5, 10]. There was no clinically relevant difference in exposure when lazertinib was administered with food compared with the fasted state; therefore, lazertinib can be administered with or without food [5]. Following a single dose of lazertinib 240 mg, systemic exposure to lazertinib was similar in healthy subjects and in patients with NSCLC [5].

The average volume of distribution of lazertinib was 4263.97 L after a single dose of lazertinib 240 mg in patients with NSCLC, indicating that lazertinib was widely distributed in the body [5]. In vitro plasma protein binding of lazertinib was 99.1–99.7%.

Based on in vitro studies, the main metabolic pathway of lazertinib was glutathione conjugation by glutathione S-transferase M1, and metabolism mainly by CYP3A4 played a minor role [5]. In patients with NSCLC, metabolites accounted for < 10% of drug-related exposure at steady state [5]. Lazertinib is largely excreted in bile and faeces; after administration of a radioactive dose of lazertinib in rodents, 60, 24 and 4.4% of the dose was recovered in the bile, faeces and urine, respectively [5]. After a single dose of lazertinib 240 mg in patients with NSCLC, the plasma concentration of lazertinib decreased bi-exponentially, with a mean terminal half-life of 64.7 h [5, 10].

Features and properties of lazertinib	
Alternative names	GNS-1480; JNJ 73841937; JNJ-1937; lazertinib mesylate monohydrate; LECLAZA®; YH25448
Class	Amides; aniline compounds; antineoplastics; dimethylamines; ethers; morpholines; pyrimidines; small molecules
Mechanism of action	EGFR tyrosine kinase inhibitor
Route of administration	Oral
Pharmacodynamics	Highly selective for *EGFR* single (Ex19del, L858R, T790M) and double (Ex19del/T790M and L858R/T790M) mutations
	High blood-brain permeability and more effective than osimertinib in inducing tumour regression in an *EGFR*-mutated mouse brain metastasis model
	Potent antitumour activity in a patient-derived xenograft model of *EGFR*-mutant NSCLC and in a patient with *EGFR*-mutant NSCLC
Pharmacokinetics	Median time to peak plasma concentration 2–4 h; steady state reached by day 15
	Average volume of distribution 4263.97 L; highly plasma protein bound (99.1–99.7%)
	Mean terminal half-life of 64.7 h; excreted largely in bile (60%) and faeces (24%)
Most common adverse reactions (240 mg dose)	Rash, itchiness, paresthesia, muscle spasms, headache, diarrhoea, decreased appetite
ATC codes	
WHO ATC code	L01EB (EGFR tyrosine kinase inhibitors)
EphMRA ATC code	L1H2 (protein kinase inhibitor antineoplastics, EGFR)
Chemical name	*N*-{5-[(4-{4-[(dimethylamino)methyl]-3-phenyl-1H-pyrazol-1-yl}pyrimidin-2-yl)amino]-4-methoxy-2-(morpholin-4-yl) phenyl}prop-2-enamide

EGFR epidermal growth factor receptor

2.3 Therapeutic Trials

2.3.1 LASER201 Phase 1/2 Study

Lazertinib monotherapy demonstrated meaningful clinical activity in patients with locally advanced or metastatic NSCLC harbouring an activating *EGFR* mutation (L858R, Ex19del, G719X or L861Q) and progressing on or after EGFR TKI therapy in the first-in-human, open-label, phase 1/2 LASER201 study (comprising parts A–C NCT03046992 and part D NCT04075396) [10]. Part A is a dose-escalation cohort, part B a dose-expansion cohort, part C a dose-extension cohort and part D a safety and efficacy ex-Korea cohort. Eligible patients (aged ≥ 20 years) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 with no deterioration over the previous 2 weeks, ≥ 1 measurable extracranial lesion [according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1] and a minimum life expectancy of 3 months. Central confirmation of tumour T790M mutation status was required for the dose-escalation cohort ($n = 38$), and the tumours had to be T790M-positive for the dose-expansion cohort ($n = 89$); a Cobas *EGFR* mutation test (version 2; Roche) was used to determine mutation status. At the time of data cutoff (26 November 2018), patients had received a median of 13 cycles of treatment and the median duration of treatment was 9.7 months. In the dose-escalation cohort, patients received lazertinib 20–320 mg in seven dose-escalation groups ($n = 3$–6 per group) according to a rolling six design. The maximum tolerated dose was not reached. In the dose expansion cohort, five dose groups (40–240 mg) were expanded and, based on dose-response relationship for activity and safety, lazertinib 240 mg once daily dose was selected for the extension cohort [10].

Across parts A–C of the study, 78 patients (median age 61 years; 60% female) received lazertinib 240 mg once daily, of whom 76 patients with centrally confirmed T790M-positive tumours were included in the efficacy analysis (evaluable population) [11]. At the time of data cutoff (30 Sep 2019), the median duration of follow-up was 9.6 months and 44 patients (56%) remained on treatment. In the evaluable population, the independent central review (ICR)-assessed objective response rate (ORR) was 57.9% (44/76), with two complete responses (CRs) and 42 partial responses (PRs); the disease control rate (DCR) was 89.5% (68/76). The ICR-assessed median progression-free survival (PFS) was 11.0 months and the duration of response (DOR) was 13.8 months. The investigator-assessed ORR was 72.4%, DCR was 94.7%, median PFS was 13.2 months and median DOR was 11.8 months [11].

Across all dose levels in the T790M-positive patients ($n = 162$), the ICR-assessed ORR was 59% and median PFS was 10.9 months; the investigator-assessed ORR and PFS were 68% and 11.0 months, respectively [5].

In the 22 patients with measurable brain lesions, the ICR-assessed intracranial ORR was 54.5% and the intracranial DCR was 90.9%; investigator-assessed intracranial ORR was 55% [5, 12]. The median ICR- and investigator-assessed intracranial PFS were not reached. In patients with measurable and/or non-measurable brain lesions ($n = 64$), at a median follow-up of 10.9 months, the intracranial DCR was 90.6% and the median intracranial PFS was not reached [12]. Of the 181 patients who had received at least one dose of lazertinib across all dose levels (20–320 mg), brain was the first site of disease progression by existing and/or new lesions in 13 (7.2%) of patients [12].

2.3.2 Phase 1/1b Study

An ongoing, open-label, multicentre study dose-escalation and dose-expansion phase 1/1b study (NCT04077463) is evaluating the safety, tolerability and pharmacokinetics of lazertinib as monotherapy (phase 1 dose escalation) and in combination with the EGFR-MET bispecific antibody amivantamab (phase 1b dose escalation and expansion parts A, B and C) in Japanese patients with advanced EGFR-mutated NSCLC [13]. The study has enrolled 11 patients in the phase 1 dose-escalation cohort and three patients in the phase 1b combination therapy cohort. In the dose-escalation phase, no dose limiting toxicity was reported and the recommended phase 2 dose of lazertinib was confirmed as 240 mg once daily. Patients are currently being enrolled in the 1b dose-expansion cohort A to further characterize the safety, tolerability, and preliminary antitumor activity of lazertinib 240 mg once daily and amivantamab 1050 mg (1400 mg for patients ≥ 80 kg) intravenously once weekly for the first 28-day cycle and biweekly thereafter [13].

2.3.3 CHRYSALIS Phase 1 Study

Lazertinib in combination with amivantamab demonstrated promising clinical activity in the open-label, phase 1 dose-escalation (part 1) and dose-expansion (part 2) CHRYSALIS study (NCT02609776) that is evaluating the efficacy and safety of amivantamab with and without lazertinib in patients with advanced NSCLC harbouring *EGFR* Exon 19del or L858R activating mutations [14]. Results for the combination therapy cohort are discussed here. As of 17 March 2020, 71 patients (median age 61 years) had received combination therapy. Part 1 of the study enrolled patients who had progressed after prior standard of care therapy or were ineligible for, or had refused, all other currently available therapeutic options ($n = 26$) [14, 15]. The recommended phase 2 combination dose was determined to be lazertinib

240 mg once daily plus amivantamab 1050 mg (1400 mg for patients ≥ 80 kg) [14]. As of 30 April 2020 (median treatment duration 8.2 months) in 23 patients with measurable disease, the ORR was 43.5% (10 PRs) and nine patients had stable disease. Treatment was ongoing in 13 patients at the time of assessment, [14].

Antitumour activity of lazertinib plus amivantamab combination therapy was also seen in the ongoing part 2 expansion cohort involving patients with measurable disease who were osimertinib-resistant, chemotherapy-naïve ($n = 45$), or treatment naïve ($n = 20$) [14]. At a median follow-up of 4 months, the ORR in the osimertinib-resistant cohort was 36% (1 CR and 15 PRs, one pending confirmation) and the clinical benefit rate was 60%. At a median follow-up of 7 months, the ORR in treatment-naïve patients was 100% (20 PRs), clinical benefit rate was 100%, median time to first response was 1.5 months and the median DOR was not estimable [14].

2.4 Adverse Events

2.4.1 As Monotherapy

Lazertinib was generally well tolerated in patients with locally advanced or metastatic NSCLC harbouring an activating EGFR mutation and progressing on or after EGFR TKI therapy, based on results from the pivotal, phase 1/2 LASER201 study (NCT03046992) [5, 11]. Among patients receiving lazertinib 240 mg once daily ($n = 78$), most patients had adverse reactions occurred (96.7%), which were mostly mild or moderate in severity (grade 1 or 2); severe adverse reactions were reported in 28.2% of patients. The most common (incidence > 20%) adverse reactions with lazertinib were rash (34.6%), itchiness (33.3%), paresthesia (32.1%), muscle spasms (25.6%), headache (24.4%), diarrhoea (21.8%) and decreased appetite (20.5%). Adverse reactions resulted in dose reductions in 12.8% of patients and discontinuation of lazertinib in 5.1% of patients [5, 11].

The tolerability profile of lazertinib across all dose levels (20–320 mg; $n = 181$) was generally similar to that observed with the lazertinib 240 mg dose, with the majority of adverse reactions of mild or moderate severity (grade 1 or 2); severe adverse reactions occurred in 24.9% of patients [5]. The most common (incidence > 20%) adverse reactions with lazertinib were rash (28.7%), itchiness (27.6%), constipation (22.1%) and paresthesia (21.0%). Two cases of interstitial pneumonia (one serious adverse reaction) were reported in two patients. Adverse reactions resulted in dose reductions in 8.3% of patients discontinuation of lazertinib in 3.9% of patients [5]. Lazertinib had no clinically relevant effects on corrected QT interval and left ventricular ejection fraction in patients with locally advanced or metastatic NSCLC harbouring EGFR mutations [16].

2.4.2 In Combination with Amivantamab

Lazertinib in combination with amivantamab was also generally well tolerated in patients with advanced NSCLC harbouring *EGFR* Exon 19del or L858R activating mutations in interim safety data from the phase 1 CHRYSALIS study (NCT02609776) [14]. Adverse events (AEs) were reported in all combination therapy recipients across the dose escalation and expansion phases of the study ($n = 91$), with the majority of adverse events of mild or moderate severity. Grade ≥ 3 treatment-related AEs were reported in 11% of patients and treatment-related serious AEs in 6% of patients. The most common (incidence > 20%) AEs with lazertinib

Key clinical trials of lazertinib in non-small cell lung cancer

Drug(s)	Phase	Status	Location(s)	Identifier	Sponsor
Lazertinib, Osimertinib, amivantamab, placebo	3	Recruiting	Multinational	NCT04487080; MARIPOSA; 2020-000743-31	Janssen R&D, LLC
Lazertinib, gefitinib, placebo	3	Recruiting	Multinational	NCT04248829; LASER301; YH25448-301	Yuhan Corporation
Lazertinib	1/2	Active, not recruiting	Republic of Korea	NCT03046992; LASER201; YH25448-201	Yuhan Corporation
Lazertinib	1/2	Active, not recruiting	USA, UK, Spain	NCT04075396; YH25448-201; 2019-003106-28	Janssen R&D, LLC
Lazertinib, amivantamab, carboplatin, pemetrexed	1	Recruiting	Multinational	NCT04077463; 2020-000747-31	Janssen R&D, LLC
Lazertinib, amivantamab, carboplatin, pemetrexed	1	Recruiting	Multinational	NCT02609776; CHRYSALIS; 2018-003908-38	Janssen R&D, LLC
Lazertinib	EAP	Available	Republic of Korea	NCT04829422; LASER-EAP	Yuhan Corporation

EAP Early Access Program

plus amivantamab were rash (85%), infusion-related reaction (IRR; 65%), paronychia (53%), hypoalbuminemia (37%), stomatitis (33%), pruritis (28%) and nausea (28%). Treatment-related AEs led to dose interruption or dose reduction of either one or both drugs in 19% of patients each, and 6% of discontinued either one or both drugs because of treatment-related AEs. Three patients died because of AEs, with one death considered treatment related. The tolerability profile of combination therapy was generally similar between osimertinib-resistant and treatment-naïve patients [14].

The median time to onset of rash was 16 days and the median duration of rash was 29 days; grade 3 rash occurred in 4% of patients, with one patient discontinuing treatment because of the adverse event [14]. The majority of IRRs occurred during the first infusion (65%); IRRs did not result in treatment discontinuation, nor did they impact subsequent dosing [14].

2.5 Ongoing Clinical Trials

In addition to the ongoing studies discussed in Sect. 2.3, the randomized, multicentre, phase 3 MARIPOSA study (NCT04487080) is recruiting ≈ 1000 patients to evaluate the efficacy of lazertinib plus amivantamab combination therapy versus that of osimertinib or lazertinib in patients with locally advanced or metastatic NSCLC harbouring an activating *EGFR* mutation (L858R or Ex19del) who are treatment-naïve and have measurable disease that is not amenable to curative therapy [17]. Patients with asymptomatic or previously treated and stable brain metastases are permitted in the study. The primary endpoint is PFS, and secondary endpoints include overall survival, ORR and DOR [17]. Also underway is the randomized, double-blind, phase 3 LASER301 study (NCT04248829) that will evaluate the efficacy and safety of lazertinib as first-line therapy in patients with locally advanced or metastatic NSCLC harbouring *EGFR* mutations. The study is recruiting ≈ 380 patients; the primary endpoint is PFS, and secondary endpoints include ORR, DOR, OS and intracranial PFS.

An Early Access Program of lazertinib is available in the Republic of Korea (NCT04829422) to provide access to lazertinib for adults with locally advanced or metastatic NSCLC with *EGFR* T790M mutation and who are progressing after first- or second-generation EGFR TKI Therapy.

3 Current Status

Lazertinib received its first approval on 18 January 2021 therapy in the Republic of Korea for the treatment of patients with *EGFR* T790M mutation-positive locally advanced or metastatic NSCLC who have previously received EGFR-TKI [4, 5].

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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