Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study

Anthony R Mato, Nirav N Shah, Wojciech Jurczak, Chan Y Cheah, John M Pagel, Jennifer A Woyach, Bita Fakhri, Toby A Eyre, Nicole Lamanna, Manish R Patel, Alvaro Alencar, Ewa Lech-Maranda, William G Wierda, Catherine C Coombs, James N Gerson, Paolo Ghia, Steven Le Gouill, David John Lewis, Suchitra Sundaram, Jonathon B Cohen, Ian W Flinn, Constantine S Tam, Minal A Barve, Bryone Kuss, Justin Taylor, Omar Abdel-Wahab, Stephen J Schuster, M Lia Palomba, Katharine L Lewis, Lindsey E Roeker, Matthew S Davids, Xuan Ni Tan, Timothy S Fenske, Johan Wallin, Donald E Tsai, Nora C Ku, Edward Zhu, Jessica Chen, Ming Yin, Binoj Nair, Kevin Ebata, Narasimha Marella, Jennifer R Brown, Michael Wang

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Memorial Sloan Kettering Cancer Center, New York, NY, USA (A R Mato MD, O Abdel-Wahab MD, M L Palomba MD, L E Roeker MD); **Medical College of Wisconsin, Brookfield, WI, USA** (N N Shah MD); **Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland** (W Jurczak MD); **Linear Clinical Research and Sir Charles Gairdner Hospital and University of Western Australia, Perth, WA, Australia** (C Y Cheah MBBS, K L Lewis MBBS, X N Tan MD); **Center for Blood Disorders and Stem Cell Transplantation, Swedish Cancer Institute, Seattle, WA, USA** (J M Pagel MD); **The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA** (J A Woyach MD); **Division of Hematology and Oncology, University of California, San Francisco, CA, USA** (B Fakhri MD); **Churchill Cancer Center, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (T A Eyre MD); **Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA** (N Lamanna MD); **Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL, USA** (M R Patel MD); **Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, FL, USA** (A Alencar MD, J Taylor MD); **Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland** (E Lech-Maranda MD); **MD Anderson Cancer Center, Houston, TX, USA** (W G Wierda MD, M Wang MD); **Lineberger Comprehensive Cancer Center, University of**

Summary

Background Covalent Bruton's tyrosine kinase (BTK) inhibitors are efficacious in multiple B-cell malignancies, but patients discontinue these agents due to resistance and intolerance. We evaluated the safety and efficacy of pirtobrutinib (working name; formerly known as LOXO-305), a highly selective, reversible BTK inhibitor, in these patients.

Methods Patients with previously treated B-cell malignancies were enrolled in a first-in-human, multicentre, open-label, phase 1/2 trial of the BTK inhibitor pirtobrutinib. The primary endpoint was the maximum tolerated dose (phase 1) and overall response rate (ORR; phase 2). This trial is registered with ClinicalTrials.gov, NCT03740529.

Findings 323 patients were treated with pirtobrutinib across seven dose levels (25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg once per day) with linear dose-proportional exposures. No dose-limiting toxicities were observed and the maximum tolerated dose was not reached. The recommended phase 2 dose was 200 mg daily. Adverse events in at least 10% of 323 patients were fatigue (65 [20%]), diarrhoea (55 [17%]), and contusion (42 [13%]). The most common adverse event of grade 3 or higher was neutropenia (32 [10%]). There was no correlation between pirtobrutinib exposure and the frequency of grade 3 treatment-related adverse events. Grade 3 atrial fibrillation or flutter was not observed, and grade 3 haemorrhage was observed in one patient in the setting of mechanical trauma. Five (1%) patients discontinued treatment due to a treatment-related adverse event. In 121 efficacy evaluable patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) treated with a previous covalent BTK inhibitor (median previous lines of treatment 4), the ORR with pirtobrutinib was 62% (95% CI 53–71). The ORR was similar in CLL patients with previous covalent BTK inhibitor resistance (53 [67%] of 79), covalent BTK inhibitor intolerance (22 [52%] of 42), *BTK* C481-mutant (17 [71%] of 24) and *BTK* wild-type (43 [66%] of 65) disease. In 52 efficacy evaluable patients with mantle cell lymphoma (MCL) previously treated with covalent BTK inhibitors, the ORR was 52% (95% CI 38–66). Of 117 patients with CLL, SLL, or MCL who responded, all but eight remain progression-free to date.

Interpretation Pirtobrutinib was safe and active in multiple B-cell malignancies, including patients previously treated with covalent BTK inhibitors. Pirtobrutinib might address a growing unmet need for alternative therapies for these patients.

Funding Loxo Oncology.

Introduction

Covalent Bruton's tyrosine kinase (BTK) inhibitors have transformed the management of B-cell malignancies, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), Waldenström macroglobulinaemia, and marginal zone lymphoma.[1–4] Despite their efficacy, treatment failure often occurs through development of resistance or intolerance, with long-term follow-up showing cumulative discontinuation rates as high as 40%.[5]

Mechanisms of resistance to covalent BTK inhibitors vary by malignancy and remain incompletely understood. BTK C481 mutations appear to be the most common reason for covalent BTK inhibitor resistance in CLL and have also been observed more rarely in other B-cell malignancies.[1,6,7] In addition, genomic and epigenetic activation of parallel or downstream signalling pathways are implicated as resistance mechanisms in CLL and B-cell lymphomas.[8] Covalent BTK inhibitors also have low oral bioavailability, short half-lives, and high protein binding resulting in brief periods of exposure required to bind and inactivate BTK.[9,10] We postulated that in more proliferative tumours with higher rates of BTK turnover, covalent BTK inhibition might be limited by incomplete target inhibition towards the end of the dosing interval, potentially driving drug resistance.

Research in context

Evidence before this study

We searched PubMed on Nov 1, 2020, using the keywords "BTK inhibitor AND B-cell" and the article type filter "Clinical Trial", limited to English language publications. This search yielded 45 original research results. Manual review of this list identified 22 unique clinical trial reports of Bruton's tyrosine kinase (BTK) inhibitors in patients with various B-cell malignancies. All reported clinical trials involved covalent BTK inhibitors. None of these clinical trials specifically examined the activity of the BTK inhibitor under investigation in patients who had been treated with a previous BTK inhibitor. Although several phase 1/2 studies of BTK inhibitors specifically permitted enrolment of patients who had discontinued a previous BTK inhibitor for intolerance, outcomes in this rare subgroup were not independently reported.

Added value of this study

In this first-in-human phase 1/2 study, the novel, highly selective, and reversible BTK inhibitor, pirtobrutinib, showed promising efficacy and tolerable safety in patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma, mantle cell lymphoma, and Waldenström macroglobulinaemia who were previously treated with a BTK inhibitor. Patients who were heavily pretreated for whom there is no available standard therapy, and patients with BTK C481 mutations for whom previous BTK treatments had failed or patients who discontinued a previous BTK inhibitor due to intolerance also benefited from pirtobrutinib. At all tested dose levels, pirtobrutinib showed efficacy demonstrating its wide therapeutic index. These data suggest that the reversible BTK binding mode and pharmacokinetic properties of pirtobrutinib result in a clinically distinct profile with important implications for future clinical development and the treatment paradigm of these diseases.

Implications of all the available evidence

The available findings, including those from our study, demonstrate that many B-cell malignancies maintain dependence on B-cell receptor signalling mediated by BTK after progression on covalent BTK inhibitors. The efficacy of BTK inhibition delivered through the unique properties of pirtobrutinib might allow patients with these B-cell malignancies to further extend the clinical benefit delivered through BTK inhibition by permitting sequential use of inhibitors that bind through covalent and non-covalent mechanisms.

Novel in-class agents that overcome BTK inhibitor resistance and are safe, including in patients with previous BTK intolerance, are needed. To address this unmet need, pirtobrutinib (working name; formerly known as LOXO-305), an orally available, highly selective, reversible BTK inhibitor with equal low nM potency against both wild-type and C481-mutated BTK was developed.[11] Pirtobrutinib achieves greater than 300-fold selectivity for BTK versus 363 (98%) of 370 other kinases, reducing the potential for off-target toxicities (appendix p 3).[11] Pirtobrutinib was designed to achieve exposures exceeding 90% of maximal BTK inhibition concentration at trough, and thus deliver tonic inhibition throughout the dosing period, regardless of BTK turnover. Here we present the results of the first-in-human phase 1/2 study of pirtobrutinib in mature B-cell malignancies.

Methods

Study design

This first-in-human, phase 1/2, open-label, study of a novel BTK inhibitor, pirtobrutinib, was done at 27 sites (both community hospitals and academic medical centres) in six countries (Australia, France, Italy, Poland, the UK, and the USA). A three-plus-three dose escalation design was used. Additional enrolment of up to 150 patients was permitted across all dose levels, previously deemed safe by the safety review committee. During phase 2, patients were enrolled to one of six cohorts based on type of B-cell malignancy, previous therapy exposures, and BTK mutational status. Patient allocation by study phase and tumour type is shown in figure 1.

The protocol was approved by the institutional review boards or independent ethics committees overseeing each site. The study was done in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws. All patients provided written informed consent.

Patients

Full eligibility criteria are detailed in the protocol (appendix pp 28–31). Eligible patients had B-cell malignancies, and had received at least two previous lines of therapy. After the fifth protocol amendment, patients with CLL or small lymphocytic lymphoma (SLL) who had only one previous line of therapy that included a covalent BTK inhibitor were eligible. Concomitant anticoagulant (except warfarin) and antiplatelet agents and patients with controlled atrial fibrillation at time of enrolment were permitted. Patients were eligible regardless of *BTK* C481 mutational status, and were not randomly assigned.

Procedures

Pirtobrutinib was administered orally as monotherapy once daily in 28-day cycles. Seven dose levels were administered: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg once per day. Treatment continued until disease progression, unacceptable toxicity, or withdrawal. Patients with disease progression could continue treatment if deriving ongoing clinical benefit per investigator opinion. After the dose-limiting toxicity

North Carolina, Chapel Hill, NC, USA (C C Coombs MD); **Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA** (J N Gerson MD, S J Schuster MD); **Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy** (P Ghia MD); **Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes, Nantes, France** (S Le Gouill MD); **University Hospitals Plymouth NHS Trust, Plymouth, UK** (D J Lewis MD); **Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA** (S Sundaram MD); **Winship Cancer Institute, Emory University, Atlanta, GA, USA** (J B Cohen MD); **Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA** (I W Flinn MD); **Peter MacCallum Cancer Center, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia** (C S Tam MBBS); **Mary Crowley Cancer Research Center, Dallas, TX, USA** (M A Barve MD); **Flinders University Medical Centre, Bedford Park, SA, Australia** (B Kuss MBBS); **Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA** (M S Davids MD, J R Brown MD); **Medical College of Wisconsin, Milwaukee, WI, USA** (T S Fenske MD); **Loxo Oncology at Lilly, Stamford, CT, USA** (J Wallin PhD, D E Tsai MD, N C Ku MD, E Zhu PhD, J Chen MS, M Yin PhD, B Nair PhD, K Ebata PhD, N Marella PhD)

Correspondence to:
Dr Anthony R Mato, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
matoa@mskcc.org

or

Dr Michael Wang, MD Anderson Cancer Center, Houston, TX 77030, USA
miwang@mdanderson.org

See Online for appendix

period (cycle 1), intrapatient dose escalation was permitted to higher dose levels previously deemed safe.

Tumour evaluations were done every 8 weeks for the first year, every 12 weeks for the second year, and every 6 months thereafter. The overall response rate (ORR) was assessed according to established criteria for each histological subtype: International Workshop on Chronic Lymphocytic Leukemia 2018, International Workshop on

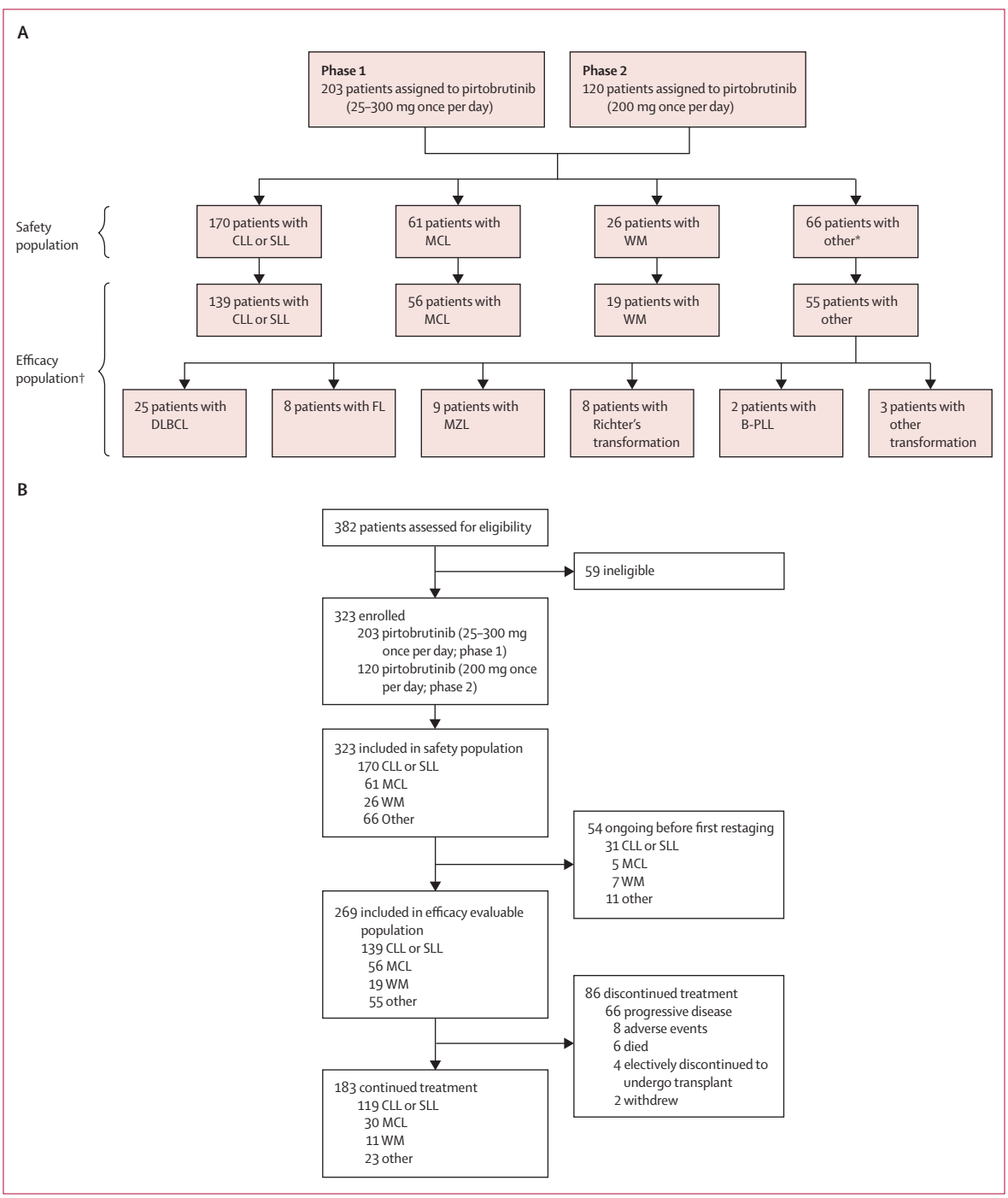

Figure 1: **Patient flow diagram (A) and CONSORT diagram (B)**
CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. MCL=mantle cell lymphoma. WM=Waldenström macroglobulinaemia. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. MZL=marginal zone lymphoma. B-PLL=B-cell prolymphocytic leukaemia. *Includes DLBCL, FL, MZL, Richter's transformation, B-PLL, hairy cell leukaemia, and other transformation. †Patients who had at least one post-baseline response assessment or had discontinued treatment before first post-baseline response assessment.

Waldenstrom's Macroglobulinemia 6, and the Lugano Treatment Response Criteria 2014. For CLL, patients with partial response with lymphocytosis were considered responders.[12] Blood samples were collected serially for pharmacokinetics analyses. Genomic analyses of peripheral blood were done as described (appendix p 2).

Outcomes

The primary endpoint for the phase 1 portion of the study was determination of the maximum tolerated dose and recommended phase 2 dose. Secondary phase 1 endpoints included ORR, pharmacokinetics, and safety. The primary endpoint for phase 2 was ORR, which was assessed by an independent review committee. Secondary endpoints were ORR as assessed by investigators, best overall response, duration of response, progression free survival, overall survival, safety and tolerability, and pharmacokinetics.

Safety was determined by frequency and severity of adverse events graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis

The data cutoff date was Sept 27, 2020. During the phase 1 dose-escalation portion of the study, three to six patients were enrolled in each cohort, as per a traditional three-plus-three design. In addition, expanded enrolment of up to a cumulative total of 150 additional patients was permitted across all dose cohorts previously declared safe by the safety review committee, to further investigate the tolerability, pharmacokinetics, and biological activity of pirtobrutinib. During phase 2, a cumulative total of 120 patients were enrolled to one of six cohorts, on the basis that approximately 20 patients per cohort would provide an 89% probability of observing at least four responders if the true underlying ORR was 30% or more.

The safety population consisted of all enrolled patients who received at least one dose of pirtobrutinib. Descriptive statistics were used to summarise the findings. The efficacy evaluable population included all patients in the safety population who had at least one post-baseline disease assessment or discontinued study treatment prior to the first response assessment. ORR was calculated in efficacy evaluable patients and a two-sided 95% CI was estimated based on the exact binomial distribution. Duration of response analysis included efficacy evaluable patients who had a response. Duration of response was estimated using the Kaplan-Meier method, with data censored at the last adequate disease assessment before the initiation of subsequent anticancer therapy. All efficacy analyses were based on investigator assessments. Statistical analyses were done using SAS, version 9.3. Prespecified overall survival and progression-free survival endpoints are not reported, as a result of statistical immaturity because of lack of events. Evaluation of ORR by histology subtype and duration of follow-up was done as a post-hoc analysis.

	All (n=323)	CLL or SLL (n=170)	MCL (n=61)	WM (n=26)	Other* (n=66)
Age, years	68 (62–74)	69 (62–73)	69 (63–75)	68 (62–74)	68 (27–86)
Sex					
Female	109 (34%)	61 (36%)	14 (23%)	8 (31%)	26 (39%)
Male	214 (66%)	109 (64%)	47 (77%)	18 (69%)	40 (61%)
ECOG PS†					
0	161 (50%)	87 (51%)	42 (69%)	14 (54%)	18 (27%)
1	139 (43%)	69 (41%)	17 (28%)	10 (39%)	43 (65%)
2	19 (6%)	13 (8%)	2 (3%)	0	4 (6%)
Number of previous lines of systemic therapy					
All patients	3 (2–5)	3 (2–5)	3 (2–4)	3 (2–4)	4 (3–5)
BTK pretreated	3 (2–5)	4 (2–5)	3 (2–4)	3 (3–4)	5 (3–7)
Previous therapy					
BTK inhibitor	245 (76%)	146 (86%)	57 (93%)	18 (69%)	24 (37%)
Chemotherapy	282 (87%)	140 (82%)	56 (92%)	23 (89%)	63 (96%)
Anti-CD20 antibody	302 (94%)	153 (90%)	60 (98%)	24 (92%)	65 (99%)
BCL2 inhibitor	81 (25%)	57 (34%)	9 (15%)	3 (12%)	12 (18%)
PI3K inhibitor	51 (16%)	36 (21%)	1 (2%)	1 (4%)	13 (20%)
Lenalidomide	45 (14%)	14 (8%)	12 (20%)	1 (4%)	18 (27%)
Autologous stem-cell transplant	22 (7%)	0	15 (25%)	0	7 (11%)
Allogeneic stem-cell transplant	8 (3%)	3 (2%)	3 (5%)	0	2 (3%)
CAR T-cell therapy	22 (7%)	10 (6%)	3 (5%)	0	9 (14%)
Reason discontinued any previous BTK inhibitor‡§					
Progressive disease	173 (71%)	98 (67%)	44 (77%)	12 (67%)	19 (79%)
Toxicity or other¶	70 (29%)	48 (33%)	13 (23%)	6 (33%)	5 (21%)

Data are median (IQR) or n (%). CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. MCL=mantle cell lymphoma. WM=Waldenström macroglobulinaemia. ECOG PS=Eastern Cooperative Oncology Group performance status. PI3K=phosphatidylinositol 3-kinase. CAR=chimeric antigen receptor. BTK=Bruton's tyrosine kinase. *Includes diffuse large B-cell lymphoma (n=26), follicular lymphoma (n=12), marginal zone lymphoma (n=13), Richter's transformation (n=9), other transformation (n=3), B-cell prolymphocytic leukaemia (n=2), and hairy cell leukaemia (n=1). †Four patients in the All category, one in CLL or SLL, two in WM, and one in Other were missing ECOG PS. ‡One MCL patient and one Richter's transformation patient had missing previous BTK inhibitor discontinuation reason. §Calculated as percentage of patients who received previous BTK inhibitor. ¶Includes patients who completed treatment and those who discontinued voluntarily or due to physician's decision. Total percentage might be different than the sum of the individual components due to rounding.

Table 1: **Patient characteristics at baseline**

This trial is registered with ClinicalTrials.gov, NCT03740529.

Role of the funding source

The study was supported by funding from Loxo Oncology, a wholly owned subsidiary of Eli Lilly and Company. Loxo Oncology conceived and designed the study protocol jointly with ARM and MW. The first draft of the Article was written by ARM and MW in collaboration with the funder.

Results

Between March 21, 2019, and Sept 27, 2020, 323 patients (170 with CLL or SLL, 61 with MCL, 26 with Waldenström macroglobulinaemia, and 66 with other B-cell lymphomas) were enrolled (figure 1). Baseline characteristics are summarised in table 1 and in the

appendix (p 9). The median age across the study was 68 years (IQR 62–74). High-risk cytogenetic and molecular features were centrally assessed in patients with CLL with sufficient available pretreatment tumour tissue, identifying 17p deletion in 20 (25%) of 81, TP53 mutation in 27 (30%) of 91, 11q deletion in 15 (19%) of 81, and unmutated IGHV in 71 (88%) of 81 (appendix p 10). Among 170 patients with CLL or SLL, the median number of previous lines of therapy was 3 (IQR 2–5) and 146 (86%) patients had received a previous BTK inhibitor, 153 (90%) an anti-CD20 antibody, 140 (82%) chemotherapy, 57 (34%) venetoclax, 36 (21%) phosphatidylinositol 3-kinase (PI3K) inhibitor, ten (6%) chimeric antigen receptor (CAR) T-cell therapy, and three (2%) allogeneic transplant. Among the 61 patients with MCL, the median number of previous lines of therapy was 3 (IQR 2–4) and 57 (93%) patients had received a previous BTK inhibitor, 60 (98%) an anti-CD20 antibody, 56 (92%) chemotherapy, 12 (20%) lenalidomide, 15 (25%) autologous transplant, three (5%) allogeneic transplant, and three (5%) CAR T-cell therapy.

Pirtobrutinib exhibited linear dose-proportional exposures (maximum concentration in plasma and area under the curve) and low interpatient variability throughout the entire dosing range of 25 mg to 300 mg daily (appendix p 4). The observed half-life was approximately 20 h. Efficacy was observed at all dose levels and safety data supported selection of a 300 mg dose. 200 mg daily, corresponding to unbound pirtobrutinib trough steady-state exposures with BTK plasma concentration corresponding to 96% target inhibition, was selected as the recommended phase 2 dose.

	Adverse events, regardless of attribution					Treatment-related adverse events	
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grades 3 or 4	Any grade
Adverse event							
Fatigue	40 (12%)	22 (7%)	3 (1%)	0	65 (20%)	2 (1%)	27 (8%)
Diarrhoea	45 (14%)	10 (3%)	0	0	55 (17%)	0	28 (9%)
Contusion	37 (12%)	5 (2%)	0	0	42 (13%)	0	29 (9%)
Neutropenia*	5 (2%)	4 (1%)	19 (6%)	13 (4%)	41 (13%)	17 (5%)	20 (6%)
Nausea	25 (8%)	5 (2%)	0	0	30 (9%)	0	10 (3%)
Cough	20 (6%)	9 (9%)	0	0	29 (9%)	0	2 (1%)
Headache	22 (7%)	5 (2%)	2 (1%)	0	29 (9%)	1 (<1%)	13 (4%)
Dyspnoea	16 (5%)	9 (3%)	1 (<1%)	0	26 (8%)	0	6 (2%)
Constipation	20 (6%)	4 (1%)	1 (<1%)	0	25 (8%)	0	6 (2%)
Anaemia	6 (2%)	6 (2%)	12 (4%)	0	24 (7%)	4 (1%)	10 (3%)
Pyrexia	19 (6%)	2 (1%)	1 (<1%)	0	23 (7%)	1 (<1%)	6 (2%)
Upper respiratory tract infection	4 (1%)	19 (6%)	0	0	23 (7%)	0	3 (1%)
Back pain	14 (4%)	8 (3%)	0	0	22 (7%)	0	2 (1%)
Peripheral oedema	18 (6%)	4 (1%)	0	0	22 (7%)	0	2 (1%)
Rash maculopapular	18 (6%)	2 (1%)	0	0	20 (6%)	0	9 (3%)
Abdominal pain	10 (3%)	7 (2%)	1 (<1%)	0	18 (6%)	0	4 (1%)
Dizziness	16 (5%)	2 (1%)	0	0	18 (6%)	0	8 (3%)
Hyperuricaemia	17 (5%)	0	0	0	17 (5%)	0	9 (3%)
Arthralgia	13 (4%)	3 (1%)	0	0	16 (5%)	0	5 (2%)
Pruritus	13 (4%)	3 (1%)	0	0	16 (5%)	0	8 (3%)
Adverse event of special interest†							
Bruising‡	48 (15%)	5 (2%)	0	0	53 (16%)	0	37 (12%)
Rash§	30 (9%)	5 (2%)	0	0	35 (11%)	0	18 (6%)
Arthralgia	13 (4%)	3 (1%)	0	0	16 (5%)	0	5 (2%)
Haemorrhage¶	10 (3%)	4 (1%)	1 (<1%)‖	0	15 (5%)	0	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	0	15 (5%)	0	4 (1%)
Atrial fibrillation or flutter	0	2 (1%)**	0	0	2 (1%)	0	0

Data are n (%). The adverse events listed are those that occurred at any grade in at least 5% of the patients. *Combines neutrophil count decreased and neutropenia. †Adverse events of special interest are those that were previously associated with covalent BTK inhibitors. ‡Bruising includes contusion, petechia, ecchymosis, and increased tendency to bruise. §Rash includes rash maculopapular, rash, rash macular, rash erythematous, rash popular, rash pruritic, and rash pustular. ¶Haemorrhage includes haematoma, epistaxis, rectal haemorrhage, subarachnoid haemorrhage, upper gastrointestinal haemorrhage, vitreous haemorrhage, and wound haemorrhage. ‖Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to pirtobrutinib. **Both events grade 2 considered by investigators as unrelated to pirtobrutinib due to a history of previous atrial fibrillation in each.

Table 2: **Adverse events in 323 patients who received pirtobrutinib**

Seven dose levels, 25 mg to 300 mg daily, were evaluated. No dose-limiting toxicities were observed and thus no maximum tolerated dose was established. All adverse events, regardless of attribution, that occurred during treatment in at least 5% of patients, as well as adverse events of special interest to BTK inhibitors are shown in table 2. Adverse events of grade 3 or higher were uncommon, with the majority (1515 [87%] of 1735 events) of all adverse events being grade 1 or 2. The most common adverse event of grade 3 or higher was neutropenia (32 [10%] of 323 patients). Neutropenia was not dose-dependent and febrile neutropenia was observed in five (1%) of 323 patients. Upper respiratory tract infections were the most common infection observed in 23 (7%) of 323 patients. There was no correlation between pirtobrutinib exposure and the frequency of grade 3 treatment-related adverse events. The safety profile was similar among patients with various tumour types (appendix p 11) and patients who received at least one dose of 200 mg pirtobrutinib (appendix p 12). Adverse events observed in at least 10% of 323 patients were fatigue (65 [20%]), diarrhoea (55 [17%]), and contusion (42 [13%]; table 2). Dose interruptions were observed in 26 (8%) patients, reductions in seven (2%) patients, and permanent discontinuations for drug-related adverse events in five (1%) patients.

Atrial arrhythmias and haemorrhage are two important adverse events associated with covalent BTK inhibitor discontinuation.[13] In the overall safety population of 323 patients, atrial fibrillation or flutter was seen in two (<1%) patients, with both events grade 2 and considered unrelated to pirtobrutinib due to a history of previous atrial fibrillation in each patient. One patient experienced a grade 3 haemorrhage, a subarachnoid bleed sustained during a bicycle accident. Frequency of bruising, seen in 53 (16%) patients, was not related to dose or exposure. In total, 18 patients had discontinued a previous BTK inhibitor for cardiovascular toxicity (n=15) or haemorrhage (n=3). None had recurrence of these events on pirtobrutinib.

Of the 323 patients treated with pirtobrutinib, 269 patients were efficacy evaluable, including 139 with CLL or SLL, 56 with MCL, 19 with Waldenström macroglobulinaemia, and 55 with other B-cell lymphomas (table 3). The 54 (17%) patients who were not included in the efficacy analysis for response were all ongoing on pirtobrutinib, progression-free, and pending their first response assessment at the time of data lock. Patients who withdrew from the protocol before a formal response assessment were efficacy evaluable and considered non-responders. At the data cutoff, 237 (73%) of 323 of all treated patients remained on pirtobrutinib (appendix p 13). Efficacy data by starting pirtobrutinib dose are presented in the appendix (p 15).

In 139 efficacy evaluable patients with CLL or SLL treated across all dose levels, the ORR was 63% (95% CI 55–71) including 69 patients with partial response, 19 with partial response with lymphocytosis, 45 with stable disease, one with progressive disease, and five discontinued before their first response assessment and were considered non-evaluable, but counted as non-responders (table 3; figure 2). In the 121 efficacy evaluable, BTK-pretreated patients, the ORR was 62% (95% CI 53–71). As expected with on-target BTK inhibition, lymphocytosis occurred early in cycle 1, preceding maximal nodal regression (appendix p 5). Consistent with this finding, responses deepened over time (figure 2). The ORR was similar in patients who previously discontinued a covalent BTK inhibitor for progression (53 [67%] of 79) versus toxicity or another reason (22 [52%] of 42). Among patients with progression on a previous covalent BTK inhibitor, the ORR was also similar in patients with a *BTK* C481 mutation (15 [75%] of 20) and patients without (18 [60%] of 30). Consistent

	Number of lines of previous systemic therapy	Treated	Efficacy, evaluable*	Responders	Overall response rate
Chronic lymphocytic leukaemia and small lymphocytic lymphoma					
All patients	3 (2–5)	170	139	88	63% (55–71)
Patients who had previous therapy					
With at least BTK	4 (2–5)	146	121	75	62% (53–71)
With at least BCL2	5 (4–7)	57	48	31	65% (50–78)
With at least PI3K	4 (3–6)	36	30	18	60% (41–77)
With at least BTK and BCL2	5 (4–7)	54	45	29	64% (49–78)
With at least chemotherapy, CD20, and BTK	4 (3–6)	113	93	62	67% (56–76)
With at least chemotherapy, CD20, BTK, and BCL2	5 (4–7)	48	39	27	69% (52–83)
With at least chemotherapy, CD20, BTK, BCL2, and PI3K	6 (4–9)	14	12	7	58% (28–85)
With at least CAR T-cell therapy	6 (4–9)	10	10	9	90% (56–100)
BTK mutational status†					
C481 mutant	3 (3–5)	25	24	17	71% (49–87)
Wild type	4 (2–4)	66	65	43	66% (53–77)
Reason for previous BTK discontinuation					
Progression	4 (3–6)	98	79	53	67% (56–77)
Toxicity or other	3 (2–4)	48	42	22	52% (36–68)
Mantle cell lymphoma					
All patients	3 (2–4)	61	56	29	52% (38–65)
Patients who received at least a BTK inhibitor	3 (2–4)	57	52	27	52% (38–66)
Waldenström macroglobulinaemia					
All patients	3 (2–4)	26	19	13	68% (44–87)
Patients who received at least a BTK inhibitor	3 (3–4)	18	13	9	69% (39–91)
Follicular lymphoma					
All patients	3 (2–6)	12	8	4	50% (16–84)

Data are median (IQR), n, or % (95% CI). PI3K=phosphatidylinositol 3-kinase. CAR=chimeric antigen receptor. *Efficacy evaluable includes patients who had at least one post-baseline response assessment or who discontinued treatment before their first post-baseline response assessment. †BTK mutational status tested centrally in 91 patients.

Table 3: **Efficacy of pirtobrutinib**

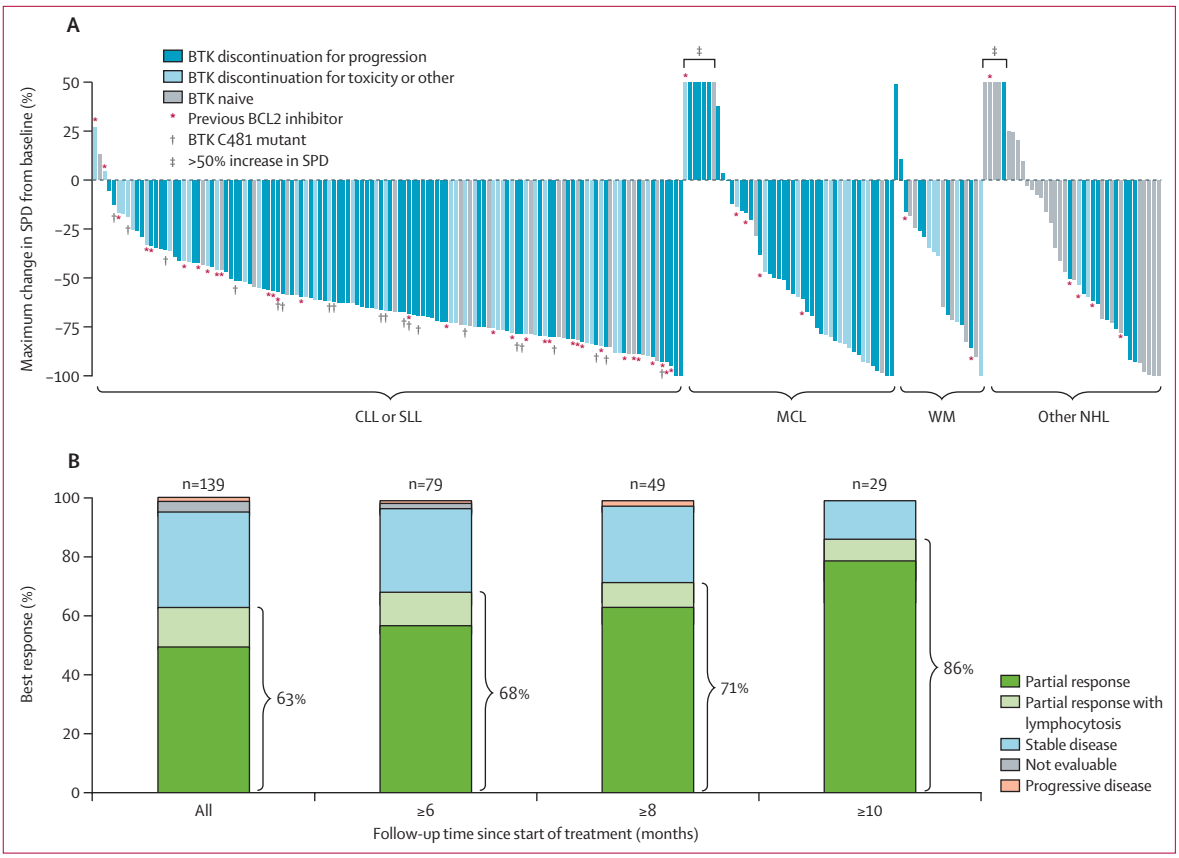

Figure 2: **Efficacy**

(A) Change in tumour burden from baseline, measured by changes in the SPD on axial CT images of index lesions for efficacy evaluable patients with CLL or SLL, or MCL, and other B-cell lymphomas. For WM, the maximum change in IgM levels from baseline are shown. Colour of bar indicates status of previous BTK inhibitor therapy and reason for discontinuation. Efficacy evaluable patients had at least one post-baseline response assessment or had discontinued treatment before first post-baseline response assessment. Data for 41 patients (13 CLL or SLL, 11 MCL, and 17 other NHLs) are not shown due to 17 having no target lesions identified at baseline, ten with no or incomplete post-baseline lesion measurements, and 14 discontinued prior to first post-baseline disease assessment. (B) Responses over time for CLL or SLL efficacy evaluable patients are shown. All includes the efficacy evaluable CLL or SLL patients at the time of data cutoff. Data at each timepoint includes the efficacy evaluable CLL or SLL patients who had the opportunity to be followed for at least the indicated amount of time. CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. SPD=sums of the products of the maximum perpendicular dimensions. MCL=mantle cell lymphoma. WM=Waldenström macroglobulinaemia. NHL=non-Hodgkin's lymphoma.

with this finding, *BTK* C481 mutant allele fraction from peripheral blood mononuclear cells decreased over time with treatment in the majority of responding patients (appendix p 6). In the 28 patients with a 17p deletion, *TP53* mutation, or both, the ORR was 79%. Detailed ORRs of patients with CLL and high molecular risk features are presented in the appendix (p 16).

88% of all patients with CLL or SLL remain on pirtobrutinib. Median follow-up for the 139 efficacy evaluable patients with CLL or SLL was 6 months (IQR 4–9; figure 3; appendix p 7). Of the 88 responding patients with CLL or SLL, all except five remained on therapy (four progressed and one had a partial response and electively discontinued). The longest followed up responding patient continues on treatment at more than 17·8 months.

In the 56 efficacy evaluable patients with MCL the ORR was 52% (95% CI 38–65), including 14 with complete response, 15 with partial response, ten with stable disease, 12 with progressive disease, and five not evaluable (table 3; figure 2). Among the 52 patients who had received a previous covalent BTK inhibitor, the ORR was also 52% (95% CI 38–66). Responses were observed in patients with MCL who received previous cellular therapy, including nine (64%) of 14 patients with previous autologous or allogeneic transplant, and two (100%) of two with previous CAR T-cell therapy. Responses were also observed in two (50%) of four patients with blastoid variant MCL. Median time to first response was 1·8 months (IQR 1·8–1·9), corresponding with first response assessment.

57% of all patients with MCL remain on pirtobrutinib. Median follow-up for efficacy evaluable patients with MCL was 6 months (IQR 3–9; figure 3; appendix p 8). Of the 29 responding patients, five discontinued treatment (four for progressive disease and one in complete

response who electively discontinued treatment to undergo allogeneic stem-cell transplant).

In 19 efficacy evaluable patients with Waldenström macroglobulinaemia, the ORR was 68%, including nine patients with partial response, four with minor response, three with stable disease, and three with progressive disease (table 3; figure 2). Among 13 patients who had received a previous covalent BTK inhibitor, the ORR was 69% (five with partial response and four with minor response). Ten (77%) of 13 patients with Waldenström macroglobulinaemia who responded to treatment are ongoing at a median follow-up of 5 months (IQR 4–6). Among eight patients with follicular lymphoma who were efficacy evaluable, responses were observed in four (50%) patients. Six (75%) of eight efficacy evaluable patients with Richter's transformation identified before enrolment responded to treatment. Responses were ongoing in five patients at the time of data cutoff, with the majority of these responding patients having undergone only one follow-up response assessment to date (appendix p 18). Of the remaining 39 efficacy evaluable patients, eight responses were observed (six of 25 patients with diffuse large B-cell lymphoma, and two of nine patients with marginal zone lymphoma; appendix p 19). Three of six diffuse large B-cell lymphoma responses were ongoing at a median follow-up duration of 4 months (appendix p 18).

Discussion

In this initial phase 1/2 trial of pirtobrutinib, a highly selective and reversible BTK inhibitor, the data show favourable safety and promising efficacy in multiple B-cell neoplasms, including heavily pretreated CLL, MCL, Waldenström macroglobulinaemia, and follicular lymphoma. Activity was seen in patients with multiple B-cell neoplasms previously treated with covalent BTK inhibitors, including patients with resistance mediated by *BTK* C481 mutations, patients with uncharacterised resistance mechanisms, and patients who discontinued their previous BTK inhibitor due to intolerance. Consistent with its highly selective profile, pirtobrutinib appeared to be well tolerated, with a wide therapeutic index, as shown by the observed efficacy at all dose levels tested and the lack of a maximum tolerated dose. To date, low rates of important BTK-mediated toxicities, including atrial arrhythmias and major bleeding, have been observed, despite permitting patients with history of these events and patients on concurrent anticoagulation. Contusions (a class effect of all BTK inhibitors) were observed, reflecting on-target BTK inhibition in platelets. Collectively, these data suggest that the reversible BTK binding mode and pharmacokinetic properties of pirtobrutinib result in a clinically distinct profile with important implications for future clinical development and the treatment paradigm of these diseases.

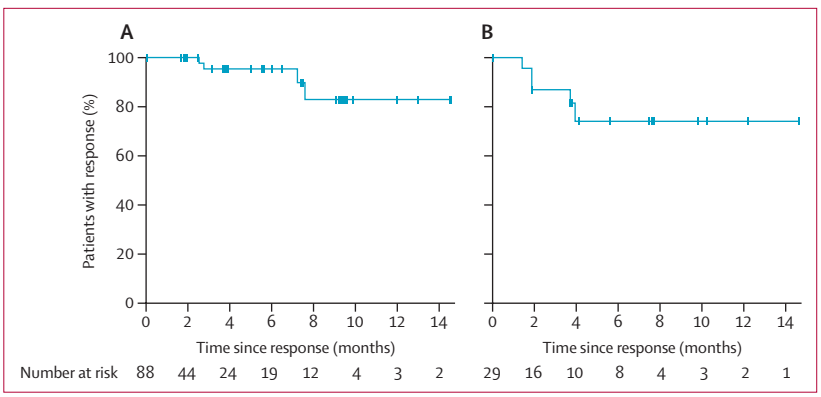

Figure 3: **Kaplan-Meier plots of duration of response in patients with CLL or SLL (A) and MCL (B)**
CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. MCL=mantle cell lymphoma.

For patients with CLL or SLL, the availability of effective and safe therapies after failure of either covalent BTK inhibitors or BCL2 inhibitors remains an area of high unmet need. The activity of chemotherapy combinations, anti-CD20 antibodies, and PI3K inhibitors after failure of covalent BTK inhibitors or venetoclax, or both, has not been evaluated prospectively, but available observational data suggest limited activity and poor tolerance.[14–21] The efficacy observed in CLL or SLL with pirtobrutinib after treatment with both covalent BTK inhibitors and venetoclax is therefore particularly noteworthy. Furthermore, unlike venetoclax, which requires a 5-week dose ramp-up with intensive monitoring, pirtobrutinib was able to be safely administered starting at a full dose without the need for such close monitoring.

Although covalent BTK inhibitors have also transformed the management of relapsed or refractory MCL, responses are generally less durable than in CLL. Specifically, in relapsed or refractory MCL, covalent BTK inhibitors have a median progression-free survival less than 2 years and median duration of response in the range of 18–24 months.[22–24] Moreover, *BTK* C481 mutations are rarely observed in MCL, with activation of parallel pathways more commonly implicated.[25,26] Following progression on BTK inhibitors, survival of patients with MCL is poor, at only 4–10 months.[27–29] Although CD19-targeted CAR T-cell therapy has recently been approved in the USA, this approach is resource intensive, limited in availability to large tertiary centres, and often associated with risk of severe toxicities that collectively limit use.[30] Moreover, CD19-targeted CAR T-cell therapy requires an effective bridging therapy, which can be difficult in BTK inhibitor-resistant patients. Thus, the activity of pirtobrutinib in relapsed, BTK-pretreated MCL is particularly promising and addresses an important unmet clinical need.

This study does have some important limitations. Given the long natural history of some B-cell malignancies, in particular CLL, longer follow-up is needed to better estimate the durability of pirtobrutinib responses. Additionally, although the safety profile of pirtobrutinib

is encouraging, longer follow-up will be needed to better understand the full safety profile of this agent associated with chronic administration.

In summary, in this first-in-human trial of pirtobrutinib, we showed promising efficacy and safety in patients with B-cell malignancies, including CLL or SLL, MCL, Waldenström macroglobulinaemia, and follicular lymphoma. Activity was observed in heavily pretreated patients, including patients with resistance and intolerance to previous covalent BTK inhibitor treatment. Global randomised phase 3 studies in CLL or SLL, and MCL are planned.

Contributors

All authors critically revised the manuscript and approved the final version. ARM and MW drafted the manuscript. ARM, MW, DET, and NCK conceptualised and designed the study. JW, DET, NCK, EZ, JC, MY, BN, KE, and NM verified and interpreted acquired study data, and did the analysis. MY and JC conducted statistical analyses. ARM, NNS, WJ, CYC, JMP, JAW, BF, TAE, NL, MRP, AA, ELM, WGW, CCC, JNG, PG, SLG, DJL, SS, JBC, IWF, CST, MAB, BK, JT, OAW, SJS, MLP, KLL, LER, MSD, XNT, TSF, JRB, and MW acquired and interpreted the study data. Susan P Whitman, employee of Loxo Oncology at Lilly, provided medical writing support. All authors had access to and verified the data. All authors vouch for the completeness and accuracy of the data and adherence to the protocol. All authors agreed to the content of the manuscript and submission.

Declaration of interests

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Data sharing

Eli Lilly provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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