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RESEARCH LETTER

Ibrutinib plus venetoclax for relapsed/refractory mantle cell lymphoma: Final analysis of the phase 3 SYMPATICO study

To the Editor,

Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, and venetoclax, a once-daily oral B-cell lymphoma 2 inhibitor, have both shown single-agent activity in patients with relapsed/refractory mantle cell lymphoma (MCL).[1–6] Ibrutinib and venetoclax have complementary mechanisms of action, and the combination showed synergistic antitumour activity in preclinical models of MCL[7,8] and high complete response (CR) rates in patients with relapsed/refractory MCL.[9,10]

The phase 3 SYMPATICO study evaluated ibrutinib + venetoclax in patients with relapsed/refractory or previously untreated MCL.[10–12] After an open-label safety run-in phase confirming the safety of concurrent initiation of ibrutinib and venetoclax,[10] a double-blind randomisation phase evaluated ibrutinib + venetoclax versus ibrutinib + placebo in patients with relapsed/refractory MCL.[11] Subsequently, an open-label cohort evaluated first-line ibrutinib + venetoclax in patients with previously untreated MCL who were ≥65 years or had *TP53* mutations.[12] Primary analysis results of the randomised phase (median follow-up, 51.2 months) showed superior progression-free survival (PFS) with ibrutinib + venetoclax versus ibrutinib + placebo (median 31.9 vs. 22.1 months) in patients with relapsed/refractory MCL (hazard ratio 0.65; 95% confidence interval [CI], 0.47–0.88; $p = 0.0052$).[11] Here, we report final analysis results from the SYMPATICO randomised phase with one additional year of follow-up since primary analysis. At data cut-off (31 July 2024), median (range) follow-up was 61.3 months (0.1–71.4).

SYMPATICO (NCT03112174) was a multinational, randomised, double-blind, placebo-controlled, phase 3 study. Detailed methods were previously reported.[11] Briefly, eligible patients ≥18 years with relapsed/refractory MCL were randomly assigned 1:1 to receive oral ibrutinib (560 mg once daily) combined with oral venetoclax (5-week ramp-up to 400 mg once daily) or oral placebo for 24 months, then continuous single-agent ibrutinib (560 mg once daily) until disease progression or unacceptable toxicity.

Response and progression were assessed clinically and using computed tomography (or magnetic resonance imaging for lesions not well visualised by computed tomography) at baseline, every 12 weeks in year 1, every 16 weeks in years 2–3 and every 24 weeks thereafter until progression or as clinically indicated. Additional assessments included bone marrow biopsies and positron emission tomography scans to confirm CR. Treatment-emergent adverse events (TEAEs) were collected during and up to 30 days after the last dose of study treatment and were graded using Common Terminology Criteria for Adverse Events, version 4.03.

The primary end-point was PFS by investigator assessment using Revised Response Criteria for Malignant Lymphoma (Lugano criteria)[13]; patients without progression or death were censored at the last adequate disease assessment. Secondary end-points included CR rate, overall response rate (ORR), time to next treatment (TTNT), overall survival (OS), duration of response and safety. Time-to-event end-points were estimated using the Kaplan–Meier method; hazard ratios were calculated by stratified Cox regression modelling, and *p* values were calculated by stratified log-rank test. Response rates were compared by rate ratios using a stratified Cochran–Mantel–Haenszel test. Efficacy was assessed in all randomised patients; safety was assessed in all patients who received ≥1 dose of study treatment.

In total, 267 patients were randomly assigned to receive ibrutinib + venetoclax (134 patients) or ibrutinib + placebo (133 patients).

In the ibrutinib + venetoclax arm, ibrutinib treatment was ongoing at study closure in 31 patients (23%); 60 patients (45%) completed the planned 2 years of venetoclax, whereas venetoclax was discontinued early in 74 patients (55%). The median (range) duration of treatment was 21.4 months (0.5–70.6) with ibrutinib and 20.5 months (0.5–26.0) with venetoclax. In the ibrutinib + placebo arm, ibrutinib treatment was ongoing at study closure in 21 patients (16%); 46 patients (35%) completed 2 years of placebo, whereas placebo was discontinued early in 86 patients (65%). The median (range) duration of treatment was 17.7 months (0.1–70.7) with ibrutinib and 15.6 months (0.1–24.8) with placebo. In both arms, disease progression was the most frequent reason for treatment discontinuation (Table S1).

At final analysis, progression or death had occurred in 77 patients (57%) in the ibrutinib + venetoclax arm and in 99 patients (74%) in the ibrutinib + placebo arm. Superiority of PFS with ibrutinib + venetoclax versus

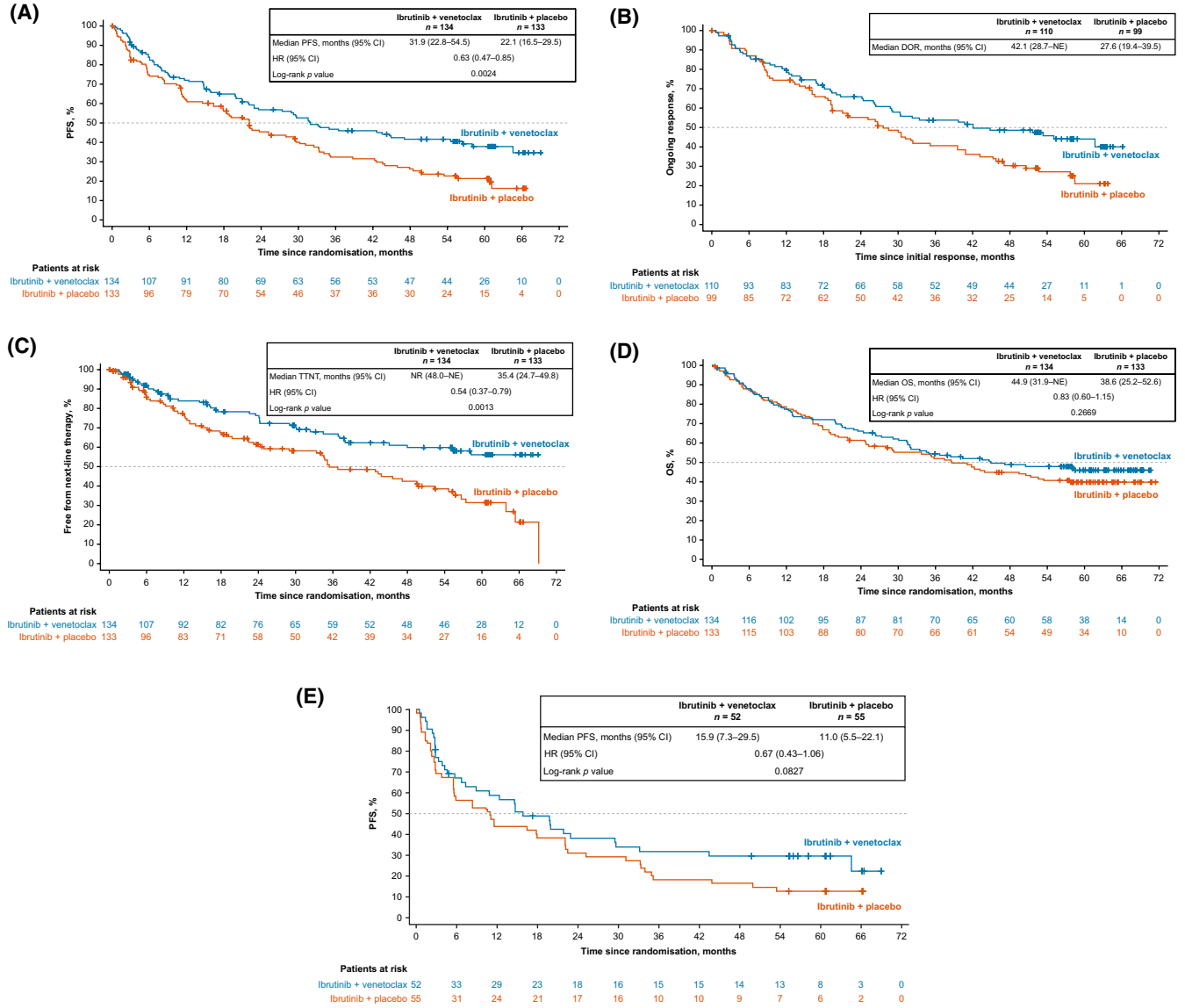

FIGURE 1 Time-to-event outcomes. Kaplan–Meier curves of (A) progression-free survival per investigator assessment in the intention-to-treat population, (B) duration of response per investigator assessment in patients who achieved partial response or better, (C) time to next treatment in the intention-to-treat population, (D) overall survival in the intention-to-treat population and (E) progression-free survival in patients with POD24 after prior first-line therapy. For progression-free survival, patients without progression or those who had not died were censored at the last adequate disease assessment. Tick marks indicate censored patients. CI, confidence interval; DOR, duration of response; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months; TTNT, time to next treatment.

ibrutinib + placebo was confirmed with a hazard ratio of 0.63 (95% CI, 0.47–0.85; $p = 0.0024$) (Figure 1A); median (95% CI) PFS was unchanged from the primary analysis: 31.9 months (22.8–54.5) vs. 22.1 months (16.5–29.5). The PFS benefit remained generally consistent across patient subgroups (Figure S1), including those with *TP53* mutations (median [95% CI] PFS: 19.8 months [8.9–33.1] vs. 10.9 months [4.5–17.9]).

Consistent with the primary analysis, a statistically significant improvement in the CR rate (95% CI) with ibrutinib + venetoclax versus ibrutinib + placebo was maintained at the final analysis: 54% (45–62) vs. 32% (24–41); rate ratio 1.66 (95% CI, 1.24–2.22); $p = 0.0004$. The ORR (95% CI) remained unchanged and showed no statistically significant difference with ibrutinib + venetoclax versus ibrutinib + placebo (82% [75–88] vs. 74% [66–82]; rate ratio 1.10 [95% CI, 0.97–1.25]; $p = 0.1279$). With additional follow-up, the median (95% CI) duration of CR was not reached (55.1 months to not estimable [NE]) vs. 44.4 months (29.0–NE) (Figure S2); the median (95% CI) duration of response was 42.1 months (28.7–NE) vs. 27.6 months (19.4–39.5) (Figure 1B).

Next-line treatment was started by 44 patients (33%) in the ibrutinib + venetoclax arm and by 69 patients (52%) in the ibrutinib + placebo arm at final analysis. Rituximab, bendamustine and cytarabine was the most frequent next-line treatment in both arms, resulting in CR in ~50% of cases (Table S4). Consistent with the primary analysis, a statistically significant improvement in TTNT was observed

for ibrutinib + venetoclax versus ibrutinib + placebo (hazard ratio, 0.54 [95% CI, 0.37–0.79]; $p = 0.0013$) (Figure 1C). Median (95% CI) TTNT was not reached (48.0 months–NE) vs. 35.4 months (24.7–49.8).

At final analysis, death had occurred in 70 patients (52%) in the ibrutinib + venetoclax arm (1 additional death since the primary analysis, due to worsening of general conditions) and in 78 patients (59%) in the ibrutinib + placebo arm (3 additional deaths, 2 due to progression, 1 due to circulatory arrest). The hazard ratio for OS at final analysis was 0.83 (95% CI, 0.60–1.15; $p = 0.2669$), reinforcing the primary analysis outcome (Figure 1D). Median OS remained unchanged (44.9 months [95% CI, 31.9–NE] with ibrutinib + venetoclax vs. 38.6 months [95% CI, 25.2–52.6] with ibrutinib + placebo).

Progression of disease within 24 months (POD24) is an independent predictor of worse OS in patients with MCL.[14] In SYMPATICO, POD24 after first-line therapy was identified (based on date of progression or start of next-line therapy) in 52 vs. 55 patients in the ibrutinib + venetoclax versus ibrutinib + placebo arms. Among these patients, median (95% CI) PFS was 15.9 (7.3–29.5) vs. 11.0 (5.5–22.1) months (Figure 1E), median (95% CI) OS was 23.2 (12.7–50.5) vs. 17.1 (12.0–35.7) months, ORR (95% CI) was 69% (55–81) vs. 64% (50–76), and CR rate (95% CI) was 38% (25–53) vs. 24% (13–37) (Table S2). Although not statistically significant, these data suggest an advantage with ibrutinib + venetoclax versus ibrutinib + placebo in patients with a history of early progression. Outcomes in patients who achieved minimal residual disease (MRD)-negative remission are in Table S3.

No new safety signals were observed with longer-term follow-up. The most frequent TEAEs are described in Table 1; TEAEs of grade ≥3 occurred in 84% ($n = 113$) and 76% of patients ($n = 100$), respectively. The most common grade ≥3 TEAEs (≥10%) were neutropenia (31%), pneumonia (13%), thrombocytopenia (13%) and anaemia (10%) with ibrutinib + venetoclax and worsening of MCL (12%), neutropenia (11%) and pneumonia (11%) with ibrutinib + placebo. No new grade 5 TEAEs were reported since the primary analysis in either arm.

With a median follow-up of 5 years, final analysis results from SYMPATICO confirmed that ibrutinib + venetoclax provides long-term benefits in patients with relapsed/refractory MCL. Having met the primary end-point at the primary analysis with a statistically significant improvement in PFS with ibrutinib + venetoclax versus ibrutinib + placebo,[11] the hazard ratio for PFS slightly improved from 0.65 at primary analysis to 0.63 at final analysis. Robustness of statistically significant improvements in CR rate and TTNT observed at the primary analysis was also confirmed by these final analysis results. As at the primary analysis, OS was numerically but not statistically significantly improved with ibrutinib + venetoclax versus ibrutinib + placebo; the hazard ratio for OS improved from 0.85 at primary analysis to 0.83 at final analysis. The safety profile remained largely unchanged from the primary analysis and was consistent with known safety profiles of the individual agents. In the absence of a statistically significant OS benefit, the benefits of combination treatment should be weighed against the risks for each patient. While ibrutinib is not approved for the treatment of MCL in the United States, the ibrutinib + venetoclax combination is currently approved for the treatment of relapsed/refractory MCL in several countries.

In conclusion, ibrutinib + venetoclax is an all-oral, once-daily, chemotherapy-free regimen with a favourable

TABLE 1 Treatment-emergent adverse events.

AE, *n* (%)	Ibrutinib + venetoclax, *n* = 134	Ibrutinib + placebo, *n* = 132
AEs of any grade	134 (100)	131 (99)
Grade ≥3 AEs	113 (84)	100 (76)
Serious AEs	88 (66)	80 (61)
AEs leading to discontinuation	43 (32)	48 (36)
Ibrutinib only	15 (11)	11 (8)
Venetoclax/placebo only	2 (1)	7 (5)
Both	26 (19)	30 (23)
AEs leading to dose reduction	50 (37)	29 (22)
Ibrutinib only	19 (14)	14 (11)
Venetoclax/placebo only	13 (10)	7 (5)
Both	18 (13)	8 (6)
AEs leading to death	22 (16)	18 (14)
Most frequent any-grade AEs[a]		
Diarrhoea	86 (64)	47 (36)
Neutropenia	46 (34)	19 (14)
Nausea	42 (31)	22 (17)
Fatigue	39 (29)	37 (28)
Anaemia	33 (25)	16 (12)
Cough	28 (21)	36 (27)
Pyrexia	28 (21)	26 (20)
Vomiting	27 (20)	15 (11)
Muscle spasms	12 (9)	32 (24)
Most frequent grade ≥3 AEs[b]		
Neutropenia	42 (31)	14 (11)
Pneumonia	17 (13)	14 (11)
Thrombocytopenia	17 (13)	10 (8)
Anaemia	14 (10)	4 (3)
Diarrhoea	11 (8)	3 (2)
Leukopenia	10 (7)	0
MCL	9 (7)	16 (12)
Atrial fibrillation	7 (5)	7 (5)
COVID-19	7 (5)	1 (1)
Hypertension	6 (4)	12 (9)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MCL, mantle cell lymphoma.

[a]Occurring in ≥20% of patients in either arm.

[b]Occurring in ≥5% of patients in either arm.

risk–benefit profile that provides durable PFS and CR rates with a positive trend for OS in long-term follow-up in patients with relapsed/refractory MCL and may represent a new treatment option for these patients.

AUTHOR CONTRIBUTIONS

Marek Trneny: Writing – review and editing; resources; investigation. **Mary-Margaret Keating:** Writing – review and editing; resources; investigation. **Frederic Peyrade:** Writing – review and editing; resources; investigation. **Nilanjan Ghosh:** Writing – review and editing; resources; investigation. **Catherine Thieblemont:** Writing – review and editing; resources; investigation. **Tom van Meerten:** Writing – review and editing; resources; investigation. **Ruben Fernandez Alvarez:** Writing – review and editing; resources; investigation. **David Belada:** Writing – review and editing; resources; investigation. **Marc Hoffmann:** Writing – review and editing; resources; investigation. **Tomasz Wrobel:** Writing – review and editing; resources; investigation. **Michael Wang:** Conceptualization; writing – review and editing; investigation; resources. **Marc Andre:** Writing – review and editing; resources; investigation. **Jennifer Lin:** Writing – review and editing; formal analysis; data curation. **James P. Dean:** Writing – review and editing; supervision; visualization. **Gottfried von Keudell:** Writing – review and editing; resources; investigation. **Wojciech Jurczak:** Writing – review and editing; investigation; resources. **Constantine S. Tam:** Writing – review and editing; conceptualization; investigation; resources. **Jutta K. Neuenburg:** Conceptualization; writing – original draft; methodology; supervision; visualization. **Edith Szafer-Glusman:** Writing – review and editing; formal analysis.

KEYWORDS

ibrutinib, mantle cell lymphoma, venetoclax

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CONFLICT OF INTEREST STATEMENT

Michael Wang reports honoraria from Acerta Pharma, Anticancer Association, AstraZeneca, BeiGene, BGICS, BioInvent, CAHON, Chinese Medical Association, Clinical Care Options, Dava Oncology, Eastern Virginia Medical School, Epizyme, Hebei Cancer Prevention Federation, Imedex, Janssen, Kite Pharma LLC, Miltenyi Biomedicine GmbH, Moffitt Cancer Center, Mumbai Hematology Group, NewBridge Pharmaceuticals, OMI, OncLive, Pharmacyclics LLC, an AbbVie Company, Physicians Education Resources (PER), Practice Point Communications (PPC), Scripps, The First Afflicted Hospital of Zhejiang University and TS Oncology; consulting/advisory role for AstraZeneca, Bayer Healthcare, BeiGene, BioInvent, CStone, DTRM Biopharma (Cayman) Limited, Epizyme, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Loxo Oncology, Miltenyi Biomedicine GmbH, Oncternal, Pharmacyclics and VelosBio; research funding from Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics LLC, an AbbVie Company and VelosBio; and travel/accommodation/expenses from Acerta Pharma, AstraZeneca, BioInvent, Celgene, Janssen, Juno Therapeutics, Kite, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics LLC, an AbbVie Company, Physician Education Resources (PER), VelosBio and Verastem. Wojciech Jurczak reports consulting and advisory role for and research funding from AbbVie, AstraZeneca, Janssen and Lilly. Marek Trneny reports honoraria from AbbVie, Amgen, Bristol Myers Squibb, Gilead Sciences, Janssen, MorphoSys, Novartis, Roche, SOBI, Swixx BioPharma and Takeda; consulting/advisory role for AbbVie, Amgen, Autolus, Bristol Myers Squibb, Caribou Biosciences, Genmab, Gilead Sciences, Incyte, Janssen, MorphoSys, Novartis, Roche, SOBI and Takeda; and travel/accommodation/expenses from AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Roche, SOBI and Takeda. David Belada reports consulting/advisory role for Gilead Sciences, Janssen-Cilag, Novartis, Roche and Takeda; research funding from Genmab, Janssen-Cilag, MorphoSys and Roche; and travel/accommodation/expenses from Gilead Science, Roche and Takeda. Tomasz Wrobel reports honoraria from BeiGene, Bristol Myers Squibb, Celgene, Gilead, Janssen-Cilag, Novartis, Roche, Sanofi and Takeda; consulting/advisory role for BeiGene, Bristol Myers Squibb, Celgene, Gilead, GlaxoSmithKline, Janssen-Cilag, Novartis, Pfizer, Roche, Sanofi and Takeda; research funding from Roche; and travel/accommodations/expenses from Gilead, Roche and Takeda. Nilanjan Ghosh reports honoraria from AbbVie, Adaptive Biotech, ADC Therapeutics, AstraZeneca, BeiGene, Bristol Myers Squibb, Epizyme, Genmab, Gilead Sciences, Incyte, Janssen, Kite Pharma, Lava Therapeutics, Loxo Oncology, Novartis, Pharmacyclics LLC, an AbbVie company, Roche/Genentech, Seagen and TG Therapeutics; consulting/advisory role for AbbVie, ADC Therapeutics, Adaptive Biotech, AstraZeneca, BeiGene, Bristol Myers Squibb, Genentech/Roche, Genmab, Gilead Sciences, Incyte, Janssen, Kite Pharma, Lava Therapeutics, Loxo Oncology, Novartis, Pharmacyclics LLC, an AbbVie Company, Seagen, Roche/Genentech and TG Therapeutics; speaker's bureau for AstraZeneca, Bristol Myers Squibb, Epizyme, Janssen, Kite Pharma and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, Bristol Myers Squibb, Gilead, MorphoSys, Pharmacyclics LLC, an AbbVie company and TG Therapeutics; and board of directors for Roche NHL Solutions Panel. Mary-Margaret Keating reports consulting/advisory role for AbbVie, Janssen and Roche. Tom van Meerten reports honoraria from Bristol Myers Squibb, Celgene, Gilead and Kite; consulting/advisory

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DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis datasets) as well as other information (e.g. protocols, clinical study reports, synopses or statistical analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP) and execution of a Data Use Agreement (DUA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select 'Home'.

ETHICS STATEMENT

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and provisions of the Declaration of Helsinki. The protocol and amendments were approved by independent ethics committees at each site.

PATIENT CONSENT STATEMENT

All patients provided written informed consent.

CLINICAL TRIAL REGISTRATION

This study is registered with ClinicalTrials.gov, NCT03112174.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.