Bimekizumab safety in patients with moderate-to-severe plaque psoriasis: pooled data from up to 3 years of treatment in randomized phase III trials

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Abstract

Background Patients with psoriasis require long-term management; therefore, understanding the long-term safety of new treatments, such as bimekizumab (BKZ), is crucial.

Objectives To evaluate BKZ’s 3-year safety profile in patients with moderate-to-severe plaque psoriasis.

Methods Three years of safety data were pooled from three phase III trials (BE VIVID, BE READY and BE SURE) and their ongoing open-label extension (BE BRIGHT). Treatment-emergent adverse events (TEAEs) are reported using exposure-adjusted incidence rates (EAIRs) per 100 patient-years (PY).

Results In total, 1495 patients received at least one BKZ dose; total BKZ exposure was 3876.4 PY. The overall EAIR of TEAEs was 175.5/100 PY and decreased with longer exposure to BKZ. The most commonly reported TEAEs were nasopharyngitis, oral candidiasis and upper respiratory tract infection (EAIRs of 15.0/100 PY, 10.1/100 PY and 6.5/100 PY, respectively); 99.3% of oral candidiasis events were mild or moderate in severity, none were serious and few led to discontinuation. EAIRs of other TEAEs of interest were low, including serious infections (1.2/100 PY), adjudicated inflammatory bowel disease (0.2/100 PY) and laboratory elevations in aspartate aminotransferase or alanine aminotransferase (> 5 × upper limit of normal: 0.6/100 PY).

Conclusions In these analyses pooled across 3 years, no new safety signals were observed with longer exposure to BKZ. The vast majority of oral candidiasis events were mild or moderate in severity, as reported previously.


What is already known about this topic?

- Individuals with moderate-to-severe plaque psoriasis require long-term management; therefore, the long-term safety of biologics must be determined.
- Previously, 2-year data pooled from phase II and III trials have demonstrated that bimekizumab (BKZ) is well tolerated.

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Psoriasis is a chronic inflammatory systemic disease placing significant burden on patients’ health and quality of life.\(^1\)–\(^4\) Patients with psoriasis have higher risk of type 2 diabetes, hypertension, obesity, inflammatory bowel disease (IBD), anxiety and depression than the general population.\(^5\)–\(^9\) Therefore, assessing long-term safety of psoriasis treatment is essential.

Current moderate-to-severe psoriasis treatment focuses on advanced biologic therapies, such as tumour necrosis factor (TNF)-\(\alpha\) and interleukin (IL)-23 and IL-17A inhibitors, which target key cytokines in psoriasis pathogenesis and have well-established safety profiles.\(^10\)–\(^20\) Bimekizumab (BKZ) is a monoclonal IgG1 antibody that selectively inhibits IL-17A and IL-17F.\(^21\)–\(^23\) Dual inhibition with BKZ in patients with psoriasis has resulted in superior efficacy compared with placebo, adalimumab (anti-TNF-\(\alpha\)), ustekinumab (anti-IL-12/23) and secukinumab (anti-IL-17A).\(^24\)–\(^27\) Further investigations have reported long-term maintenance of efficacy with BKZ over 3 years, as indicated by complete/near-complete skin clearance.\(^28\)

Previously, 2-year data pooled from phase II and III trials demonstrated that BKZ is well tolerated.\(^29\) Here, we report the first 3-year safety data for BKZ in patients with moderate-to-severe plaque psoriasis, pooled from three phase III trials and their open-label extension (OLE).

### Patients and methods

#### Patients

Safety data were pooled from three completed phase III trials: BE VIVID (NCT03370133), BE READY (NCT03410992) and BE SURE (NCT03412747), and their ongoing OLE, BE BRIGHT (NCT03598790).\(^24\)–\(^26\),\(^30\) The BE BRIGHT data cut-off was 23 October 2021, the date when the last ongoing patient reached 3 years of study treatment.

Full inclusion/exclusion criteria have been published previously.\(^24\)–\(^26\) Eligible patients for all trials were adults with moderate-to-severe plaque psoriasis, with baseline Psoriasis Area and Severity Index (PASI) \(\geq 12\), \(\geq 10\%\) body surface area affected by psoriasis and Investigator’s Global Assessment \(\geq 3\) on a 5-point scale, who were eligible for systemic psoriasis therapy and/or phototherapy.

Patients were excluded if they had active symptomatic IBD, recent (\(<\) 6 months before screening) myocardial infarction/stroke, high risk of acquiring a tuberculosis (TB) infection (or active TB infection) or active suicidal ideation \(<\) 1 month or suicide attempt \(<\) 5 years before screening.

#### Study designs

All studies were conducted in accordance with the principles of the Declaration of Helsinki and approved by an Independent Review Board and Independent Ethics Committee. All participants provided informed written consent.

Study designs for the 52-week BE VIVID trial comparing BKZ vs. placebo and ustekinumab, 56-week BE READY trial comparing BKZ vs. placebo, and 56-week BE SURE trial comparing BKZ vs. adalimumab have been published (an overview is provided in Table S1; see Supporting Information).\(^24\)–\(^26\)

Upon completion of each trial, patients were eligible to enrol in BE BRIGHT: an ongoing, multicentre, OLE study in which patients received BKZ 320 mg every 4 weeks (Q4W) or every 8 weeks (Q8W), depending on treatment, dose and PASI response at the end of the feeder study (Figure 1). Following protocol amendment, at OLE Week 48 (end of the second year of treatment) or the next scheduled clinic visit, all patients receiving BKZ Q4W switched to Q8W dosing.

#### Safety evaluations

Treatment-emergent adverse events (TEAEs), serious and severe TEAEs, and TEAEs leading to discontinuation are reported. TEAEs were defined as AEIs that occurred during exposure to treatment, including up to 140 days (five half-lives of BKZ) after the last dose was received. Serious TEAEs were TEAEs that led to at least one of the following: death, life-threatening event, substantial/persistent disability or incapacity, congenital anomaly or birth defect, important medical event and initial/extension of hospitalization. TEAEs were coded according to MedDRA version 19.0. AE intensity was assessed by investigators as mild, moderate or severe, independently from seriousness.

TEAEs of interest were infections (serious, opportunistic, TB and fungal), malignancies, major adverse cardiac events (MACE), neutropenia, suicidal ideation and behaviour (SIB), IBD, injection-site and hypersensitivity reactions, and laboratory elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) \(> 3 \times \) and \(> 5 \times\) the upper limit of normal (ULN).

Predefined cardiovascular, gastrointestinal and neuropsychiatric TEAEs were reviewed and adjudicated by independent Cardiovascular, IBD and Neuropsychiatric Adjudication Committees, respectively. SIB was assessed using the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS).\(^31\) Opportunistic infections were predefined using company conventions. Patients were screened to evaluate TB signs, symptoms and possible exposure. If a patient had a positive TB test, study treatment was stopped immediately and patients were referred to a TB specialist for further evaluation.

#### Statistical analysis

Pooled safety data were analysed, using SAS v9.4 (SAS Institute, Cary, NC, USA), for all patients who received at
least one BKZ dose in the phase III trials (BKZ Total). Safety data were also analysed separately for BKZ Q4W and Q8W treatment groups. TEAEs were attributed to the treatment and dose most recently received before the onset date.

Exposure-adjusted incidence rates (EAIRs) were used to evaluate TEAEs; EAIRs represent the number of patients with a particular AE adjusted for duration of exposure. EAIRs are reported per 100 patient-years (PY) with associated 95% confidence intervals (CIs). Psoriasis Longitudinal Assessment and Registry (PSOLAR) ranges are reported for TEAEs of interest where available.

Data are presented for the full pooled trial period for the BKZ Total group and Q4W and Q8W dosing groups, and separately for Years 1 (Weeks 0–52), 2 (Weeks >52–104) and 3 (Weeks >104–156) of BKZ exposure for the BKZ Total group. Safety data are also reported through Weeks 0–16 for patients who received BKZ during the initial placebo- or active-controlled trial periods.

Results

Patients

In total, 1495 patients received at least one BKZ dose across the phase III trials (Figure S1; see Supporting Information); baseline characteristics were similar between dosing groups and were representative of patients with plaque psoriasis eligible for biologic therapy (Table S2; see Supporting Information). Total BKZ exposure was 3876.4 PY (Q4W, 1965.6 PY; Q8W, 1914.5 PY) and median exposure duration was 1058.0 days (range, 23–1326; Table 1).

Overall safety

The EAIR of TEAEs over 3 years was 175.5/100 PY (Table 1) and decreased with each year of BKZ exposure (Figure 2). EAIRs of TEAEs during Weeks 0–16 are also reported in Table 1. EAIRs of TEAEs were numerically lower in patients receiving BKZ Q8W vs. Q4W (Table 1). Serious TEAEs and TEAEs leading to discontinuation occurred at rates of 5.5 and 3.2/100 PY, respectively (Table 1), and did not increase with longer exposure to BKZ (Figure 2). The vast majority of TEAEs were mild or moderate; the EAIR of severe TEAEs was 4.5/100 PY.

The most commonly reported TEAEs across the phase III trials by MedDRA preferred term were nasopharyngitis, oral candidiasis and upper respiratory tract infection, with EAIRs of 15.0, 10.1 and 6.5/100 PY, respectively (Table 1).

Deaths

Over 3 years, 16 deaths (0.4/100 PY) were reported (Table 1). None were reported as treatment-related by the investigators. Causes of death were reported under the following preferred terms, each for one patient unless otherwise specified (patients could have multiple preferred terms identified as leading to death): aortic aneurysm rupture, brain neoplasm, cardiac arrest (four patients), cardiopulmonary failure, chronic obstructive pulmonary disease, circulatory collapse, completed suicide, coronavirus infection (three patients), death (two patients, each of unknown cause approximately 3 months after last BKZ dose), haemorrhagic anaemia, hypovolaemic shock and myocardial infarction.
Infections
Over 3 years, the EAIRs of overall infections and serious infections (Table 2) were 81.8 and 1.2/100 PY, respectively; serious infection rates were within the PSOLAR range (0.93–2.91/100 PY). The most common serious infection was coronavirus (nine events, 0.2/100 PY). Three coronavirus events were fatal (patients had relevant comorbidities and no completed vaccination scheme); no other coronavirus events led to discontinuation. Although 17 patients had concurrent/history of latent TB and received...
### Table 2 Incidence rates of TEAEs of interest

<table>
<thead>
<tr>
<th>TEAEs of interest, EAIR/100 PY (95% CI)</th>
<th>By time period</th>
<th>Over 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BKZ 320 mg</td>
<td></td>
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<tr>
<td></td>
<td>Q4W</td>
<td>BKZ Total(^b)</td>
</tr>
<tr>
<td></td>
<td>(n = 989)</td>
<td>(n = 1456)(^b)</td>
</tr>
<tr>
<td></td>
<td>(n = 1148)</td>
<td>(n = 1289)(^b)</td>
</tr>
<tr>
<td></td>
<td>(n = 1241)</td>
<td>(n = 1495)(^b)</td>
</tr>
<tr>
<td><strong>Serious infections</strong></td>
<td>1.0 (0.2–2.9)</td>
<td>1.5 (0.9–2.3)</td>
</tr>
<tr>
<td><strong>Active tuberculosis</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fungal infections</strong></td>
<td>43.7 (36.4–52.0)</td>
<td>28.2 (25.3–31.3)</td>
</tr>
<tr>
<td><strong>Candida infections</strong></td>
<td>30.6 (24.6–37.6)</td>
<td>20.5 (18.1–23.2)</td>
</tr>
<tr>
<td><strong>Oral candidiasis</strong></td>
<td>25.3 (19.9–31.8)</td>
<td>17.6 (15.4–20.0)</td>
</tr>
<tr>
<td><strong>Oral pharyngeal candidiasis</strong></td>
<td>3.6 (1.8–6.5)</td>
<td>1.4 (0.9–2.2)</td>
</tr>
<tr>
<td><strong>Skin candidiasis</strong></td>
<td>0.7 (0.1–2.4)</td>
<td>0.6 (0.2–1.1)</td>
</tr>
<tr>
<td><strong>Vulvovaginal candidiasis</strong></td>
<td>1.3 (0.4–3.3)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td><strong>Oesophageal candidiasis</strong></td>
<td>0</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td><strong>Tinea infections</strong></td>
<td>7.3 (4.6–11.0)</td>
<td>3.6 (2.7–4.8)</td>
</tr>
<tr>
<td><strong>Fungal infections NEC(^c)</strong></td>
<td>5.0 (3.3–8.9)</td>
<td>3.9 (2.9–5.1)</td>
</tr>
<tr>
<td><strong>Adjudicated IBD</strong></td>
<td>1.0 (0.2–2.9)</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td><strong>Adjudicated MACE</strong></td>
<td>0.3 (0.0–1.6)</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td><strong>Malignancies</strong></td>
<td>1.3 (0.4–3.4)</td>
<td>0.8 (0.4–1.4)</td>
</tr>
<tr>
<td><strong>Excluding NMSC</strong></td>
<td>0.3 (0.0–1.8)</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td><strong>Adjudicated SIB</strong></td>
<td>0</td>
<td>0.1 (0.0–0.4)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>2.3 (0.9–4.7)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td><strong>AST or ALT elevations</strong></td>
<td></td>
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<tr>
<td>&gt; 3×ULN</td>
<td>4.3 (2.3–7.2)</td>
<td>2.7 (1.9–3.7)</td>
</tr>
<tr>
<td>&gt; 5×ULN</td>
<td>1.0 (0.2–2.9)</td>
<td>1.0 (0.5–1.7)</td>
</tr>
<tr>
<td><strong>Serious hypersensitivity reactions</strong></td>
<td>0</td>
<td>0.1 (0.0–0.4)</td>
</tr>
<tr>
<td><strong>Injection-site reactions</strong></td>
<td>9.0 (5.9–13.1)</td>
<td>2.9 (2.1–4.0)</td>
</tr>
</tbody>
</table>

**Data are shown as of the data cut-off date (23 October 2021). Data are pooled from the BE VIVID, BE READY and BE SURE phase III trials and their open-label extension BE BRIGHT. Data are presented for the BKZ Q4W dosing group for the initial 16-week treatment period, BKZ total and Q8W dosing groups for the full pooled trial period, and separately for Years 1 (Weeks 0–52), 2 (Weeks > 52–104) and 3 (Weeks > 104–156) of BKZ exposure for the BKZ total group. BKZ Total includes all patients who received at least one BKZ dose in the included studies; \(^a\) Includes patients who received both BKZ 320 mg Q4W and Q8W are included in the population count of both dosing groups, but only once in each BKZ Total group; \(^b\) Includes the preferred terms: anal fungal infection, ear infection fungal, fungal oesophagitis, fungal infection, fungal pharyngitis, fungal skin infection, genital infection fungal, onychomycosis, oral fungal infection, oropharyngitis fungal, tongue fungal infection and vulvovaginal mycotic infection; \(^c\) No anaphylactic reactions associated with BKZ were reported. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BKZ, bimekizumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; NEC, not elsewhere classified; NMSC, nonmelanoma skin cancer; PY, patient–years; Q4W, every 4 weeks; Q8W, every 8 weeks; SIB, suicidal ideation and behaviour; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.**
prophylactic treatment, no patients developed active TB (Table 2).

Opportunistic infections had an EAIR of 0.9/100 PY. All were localized mucocutaneous fungal infections predefined as opportunistic, except for one serious case of ophthalmic herpes zoster that resolved with treatment and did not lead to discontinuation.

Fungal infections had an EAIR of 16.7/100 PY. Most were Candida infections (11.5/100 PY); EAIRs for other fungal infections were low (Table 2).

Candidiasis

The majority of Candida infections were reported as oral candidiasis (10.1/100 PY; Table 2). Oral candidiasis EAIRs decreased with longer BKZ exposure (Figure 3), and rates were numerically lower with BKZ Q8W vs. Q4W (Table 2). The vast majority of oral candidiasis events were mild or moderate in severity (99.3%); five were severe, none were serious. One patient receiving BKZ Q4W reported a serious, severe case of oesophageal candidiasis, as previously reported.23 Rates of vulvovaginal candidiasis did not increase with longer BKZ exposure (Table 2). Seven patients discontinued BKZ due to Candida infections; five of these discontinued due to oral candidiasis (three in Year 1; three/ two while receiving Q4W/Q8W dosing, respectively).

Over the 3-year period, 154 patients (10.3%) reported one occurrence of oral candidiasis, 78 (5.2%) reported two, 38 (2.5%) reported three, 22 (1.5%) reported four and 32 (2.1%) reported five or more. Investigators determined the treatment for oral candidiasis. Most cases were treated with nystatin and/or fluconazole; median (interquartile range) duration of antifungal therapy was 12.0 (7.0–23.0) days.

Adjudicated inflammatory bowel disease

The 3-year EAIR for adjudicated definite or probable IBD was low (0.2/100 PY; Table 2). EAIRs did not increase with longer exposure to BKZ (Figure 3). In total, seven cases were adjudicated as definite (two Crohn’s disease, one ulcerative colitis, one unclassified) or probable IBD (one ulcerative colitis, two undifferentiated). Three patients had a medical history of IBD; one experienced an IBD TEAE. Five cases led to treatment discontinuation and were considered treatment-related by investigators.

Malignancies

EAIRs of malignancies excluding nonmelanoma skin cancer (NMSC) were low (0.5/100 PY; including NMSC, 0.8/100 PY; Table 2) and were within the PSOLAR range.32 Excluding NMSC, 21 occurrences of malignancies were reported in 21 patients (including NMSC, 37 occurrences in 31 patients). Malignancy EAIRs remained low with longer BKZ exposure (Figure 3). Two malignancies (one breast, one prostate) were assessed as treatment-related by investigators.

Liver function analyses

EAIRs of laboratory elevations in either AST or ALT, ALT > 3 × and > 5 × ULN were 2.1 and 0.6/100 PY, respectively, and did not increase with longer BKZ exposure (Table 2); most elevations were transient and few led to discontinuation. EAIRs of elevations > 5 × ULN were 2.7, 2.7 and 2.6/100 PY in Years 1, 2 and 3, respectively; EAIRs of elevations > 5 × ULN were 1.0, 0.4 and 0.5/100 PY.

Other treatment-emergent adverse events of interest

The EAIR of adjudicated MACE was low (0.6/100 PY) and remained low with longer BKZ exposure (Figure 3). The EAIR for adjudicated SIB was 0.1/100 PY (Table 2) and remained low with longer BKZ exposure (Figure 3). No SIB events were reported in the third year of treatment. One suicidal ideation event and one completed suicide from the first 2 years of treatment were previously reported; neither were treatment-related.28 Since the previously reported 2-year safety analyses,29 one further patient with a history of anxiety and depression, and concurrent substance abuse,
experienced adjustment disorder with depressed mood and abnormal eC-SSRS score in the second year of BKZ exposure, and was adjudicated as having suicidal ideation. The EAIR of the high-level term ‘depressive disorders’ was low (0.4/100 PY). Neutropenia rates were low (0.4/100 PY); none were temporally associated with serious infections. Rates of injection-site reactions (1.8/100 PY) and serious hypersensitivity reactions (0.1/100 PY) were low (Table 2); no anaphylactic reactions were reported.

Discussion

These analyses reported 3-year safety data for patients with moderate-to-severe plaque psoriasis who received BKZ, pooled to include three phase III trials and their OLE. Over 3 years of treatment, EAIRs of TEAEs decreased with longer exposure to BKZ (Year 1: 221.6/100 PY; Year 2: 150.6/100 PY; Year 3: 103.7/100 PY) and were lower in patients who received BKZ Q8W vs. Q4W. Discontinuations due to TEAEs were low throughout. A video summarizing the main findings of this analysis is available (Video S1; see Supporting Information).

The most common TEAEs reported with BKZ were nasopharyngitis, oral candidiasis and upper respiratory tract infection, consistent with previous reports.24–29 Individuals with psoriasis have a higher risk of infection than the general population and the use of biologics and systemic treatments may increase this risk, as well as the risk of serious infections.4,33–35 However, the EAIR of serious infections in this analysis was low (1.2/100 PY), did not increase with longer BKZ exposure, and was within the PSOLAR range (0.9–2.9/100 PY).32 Serious infection rates were also comparable with studies investigating other IL-17 inhibitors, such as brodalumab (1.0–1.3/100 PY),36 secukinumab (1.4–1.5/100 PY)18,36 and ixekizumab (1.3–2.3/100 PY).19,37 The most common serious infection was coronavirus infection, due to the third year of treatment taking place during the COVID-19 pandemic. No patients developed active TB, despite 17 patients having concurrent/history of latent TB and receiving prophylactic treatment.

Treatment with IL-17 inhibitors can increase the risk of oral candidiasis, due to IL-17’s defensive role against fungal infections at the oral mucosa.38–42 Furthermore, some individuals have a predisposed greater risk of oral candidiasis, including those who are elderly, smoke or have endocrine disorders or nutritional deficiencies.43 Although oral candidiasis rates with BKZ remain higher than with other IL-17 inhibitors18,36,37 EAIRs decreased with longer BKZ exposure, and were numerically lower in patients receiving BKZ Q8W vs. Q4W. Over the 3-year period, the vast majority of oral candidiasis events were mild or moderate (99.3%); few patients who experienced oral candidiasis discontinued as a result (1.5%).

Occurrences of AST and ALT elevations in this analysis did not increase with longer exposure to BKZ; most elevations were transient and few led to discontinuation. These observations were as expected for the study populations as psoriasis is linked to nonalcoholic fatty liver disease, obesity, diabetes and excessive alcohol consumption,44,45 all of which are known to affect liver function.

Other TEAEs of interest had low EAIRs over the 3-year period, such as MACE (0.6/100 PY) and malignancies (excluding NMSC; 0.5/100 PY). On rare occasion, new onset or exacerbation of IBD has been reported with other IL-17 inhibitors,46,47 but IBD rates were low with BKZ (0.2/100 PY), and were similar to those reported in previous studies of individuals with psoriasis.19,19,36,48 Those with psoriasis are also at increased risk of depression and SIB;49–51 however, EAIRs of depression and adjudicated SIB were low with BKZ throughout (0.4/100 PY and 0.1/100 PY).

This analysis is strengthened by its long-term nature and large sample size. Furthermore, these long-term safety data show lower TEAE rates with the BKZ Q8W dosing regimen, the recommended maintenance dose for most patients following initial Q4W dosing for 16 weeks,52 supporting its use in clinical practice. However, as Q8W dosing has been associated with lower rates of certain TEAEs vs. Q4W,44 and Year 3 data include a greater proportion of patients receiving Q8W dosing than Years 1 and 2, this may have contributed to the lower TEAE rates seen through Year 3. Due to the nature of the OLE, patients were not blinded during this period, so Year 2 and 3 data are subject to reporting bias. Moreover, these findings may be limited in their generalizability to real-world populations, due to minimal racial diversity in the patient populations and stringent patient exclusion criteria. OLE data may also have been affected by the COVID-19 pandemic coinciding with its second year (third year of treatment overall). Potential confounding factors, such as social isolation, mask wearing and lockdowns may have affected TEAE rates, in particular respiratory infections such as nasopharyngitis.

In these analyses pooled across 3 years of treatment from three phase III clinical trials and their OLE, BKZ demonstrated a favourable safety profile, with no new safety signals observed. The risk of AEs either remained consistent or decreased with longer BKZ exposure, and was lower with BKZ Q8W vs. Q4W.

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Conflicts of interest
A full Conflicts of Interest statement for all authors is available in Appendix S1 (see Supporting Information).

Additional statements
A video summarizing this manuscript is available as Video S1 (see Supporting Information).
Clinicaltrials.gov identifiers: NCT03370133, NCT03410992, NCT03412747 and NCT03598790.

Data availability
Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the USA and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents, which may include analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal.

Ethics statement
All studies were conducted in accordance with the principles of the Declaration of Helsinki and approved by an Independent Review Board and Independent Ethics Committee. All participants provided informed written consent.

Supporting Information
Additional Supporting Information may be found in the online version of this article at the publisher’s website.

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