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ORIGINAL RESEARCH

Efficacy, Safety, Patient Experience, and Tolerability of Risankizumab Administered by On-Body Injector for Moderate to Severe Crohn's Disease

Edward V. Loftus Jr. · Jenny Griffith · Ezequiel Neimark · Alexandra Song · Kori Wallace · Sujani Nannapaneni · Ji Zhou · Rachel Byrne · Kristina Kligys · Yinuo Pang · Xiaomei Liao · Jasmina Kalabic · Marla Dubinsky

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ABSTRACT

Introduction: In patients with moderate to severe Crohn's disease (CD), intravenous induction and subcutaneous maintenance dosing with risankizumab was efficacious and well tolerated. Long-term management of CD via self-administration of risankizumab using an on-body injector (OBI) may improve treatment adherence through convenience and ease of use.

Methods: Within the FORTIFY maintenance study, 46 patients from the United States (US) sites participated in an open-label extension Substudy and received 180 mg or 360 mg risankizumab delivered subcutaneously via OBI [360 mg (2.4 mL, 150 mg/mL) or 180 mg (1.2 mL, 150 mg/mL)]. At the Week 0 visit, patients were trained (pre-injection) by site staff, using Instructions for Use (IFU) and a training video, to self-administer risankizumab at Weeks 0 (on site), 8 (at home), and 16 (on site). Key objectives of the Substudy 4 were to assess OBI usability (observer rating of successful self-administration), hazard-free self-injection at Weeks 0 and 16, and patient rating of acceptability using the Self-Injection Assessment Questionnaire (SIAQ) at Weeks 0, 8, and 16. Additionally, the proportion of patients in clinical remission (CD Activity Index < 150) was collected at Weeks 0 and 16.

Results: All patients successfully self-administered risankizumab via OBI, including two patients who successfully self-administered with a second OBI (i.e., required two injection attempts). Acceptability of self-injection was high. Two patients ($n = 2$) experienced a use-related hazard. Stable clinical remission was observed with both risankizumab doses. Two patients experienced injection site reactions; neither was related to the OBI per investigator's assessment. Two device-related adverse events related to topical adhesive reactions were reported, both mild and resolved. No new safety risks were observed.

Conclusion: The efficacy and safety of maintenance risankizumab delivered via OBI and OBI

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E. V. Loftus Jr. (✉)
Mayo Clinic College of Medicine and Science, Rochester, MN, USA
e-mail: loftus.edward@mayo.edu

J. Griffith · E. Neimark · A. Song · K. Wallace · S. Nannapaneni · J. Zhou · R. Byrne · K. Kligys · Y. Pang · X. Liao
AbbVie Inc, North Chicago, IL, USA

J. Kalabic
AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

M. Dubinsky
Icahn School of Medicine at Mount Sinai, New York, NY, USA

usability support the use of this device in patients with moderate to severe CD.
Trial Registration: ClinicalTrials.gov identifiers NCT03105102 (FORTIFY).

Keywords: Risankizumab; Maintenance; On-body injector; Crohn's disease

Key Summary Points

Why carry out this study?

Poor medication adherence in patients with chronic, relapsing–remitting disease, such as Crohn's disease (CD), may lead to worsened disease outcomes; patient adherence to a treatment regimen may be impacted by a negative self-injection experience.

Maintenance therapy of risankizumab for CD was self-administered subcutaneously (SC) via two (180 mg) or four (360 mg) injections via pre-filled syringe (90 mg/mL) every 8 weeks in the pivotal phase 3 maintenance study

Self-administration of risankizumab [180 mg/1.2 mL or 360 mg/2.4 mL (150 mg/mL)], delivered via a single-dose pre-filled cartridge using a commercialized on-body injector (OBI) offers a more patient-friendly injection experience.

This study examined the efficacy, safety, usability, and patient experience of self-administration of risankizumab via OBI in patients with moderate to severe CD.

What was learned from the study?

All patients successfully self-administered risankizumab via the OBI and, at Week 16, were able to perform the critical tasks of OBI self-administration without further training, feedback, or intervention from site staff.

Self-administration via OBI achieved the expected risankizumab exposures at Week 16 compared to Week 0, and no new safety concerns were identified based on analysis of adverse events, immunogenicity, and product complaints.

The OBI was safe and well tolerated for its intended use and the conditions of use.

INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) affecting the entirety of the gastrointestinal tract. The chronic nature of CD necessitates long-term management and continuing medication use, with adherence to the prescribed treatment regimen being of paramount importance to realize full clinical benefit. However, for patients with chronic disease, adherence to medication is often poor [1]. Among IBD patients, poor adherence is associated with increased disease activity, relapse, loss of response to treatment, and increased health expenditure, and it can result in greater morbidity, mortality, disability, and a reduced quality of life [2–8].

Risankizumab, a fully humanized monoclonal antibody that binds with high affinity to the human IL-23 p19 subunit, has demonstrated efficacy and safety in clinical trials in patients with moderate to severe CD [9, 10]. In the pivotal phase 3 maintenance clinical trial, risankizumab 180 mg and 360 mg was administered via two (180 mg) or four (360 mg) subcutaneous (SC) injections, respectively, of a 90-mg/mL formulation delivered with a pre-filled syringe (PFS). To improve the patient-controlled self-injection experience, a formulation enabling administration of risankizumab via a single subcutaneous injection to be delivered via an on-body injector (OBI) was developed.

Here, we report the efficacy, safety, device usability, and patient experience of risankizumab administered with the OBI in adult patients with moderate to severe CD in a

Substudy (Substudy 4) of the FORTIFY phase 3 maintenance study.

METHODS

Study Design

FORTIFY (NCT03105102) was comprised of four substudies (SS). SS1 was the pivotal, phase 3, 52-week, randomized, double-blind, placebo-controlled, multicenter maintenance study to evaluate the efficacy and safety of SC risankizumab versus withdrawal (placebo SC) in patients with moderately to severely active CD who responded to risankizumab induction treatment (Fig. 1A) [10]. SS2 was an exploratory study of two different risankizumab dosing regimens as maintenance therapy in patients who responded to risankizumab induction treatment (Fig. 1A). SS3 was an open-label extension (OLE) study to evaluate the long-term safety, efficacy, and tolerability of risankizumab, and included patients who (1) completed SS1 or SS2 of FORTIFY, (2) patients who responded to induction treatment in ADVANCE (NCT03105128) or MOTIVATE (NCT03104413) studies with no final endoscopy performed due to the COVID-19 pandemic and agreed to enroll into SS3, or (3) patients who completed another AbbVie risankizumab CD study (Fig. 1A, B) [9, 10]. All patients who entered SS3 received 180 mg SC every 8 weeks (Q8w) except for patients who completed SS1 or SS2 and received risankizumab rescue therapy (one dose of 1200 mg IV, followed by 360 mg SC Q8w); these

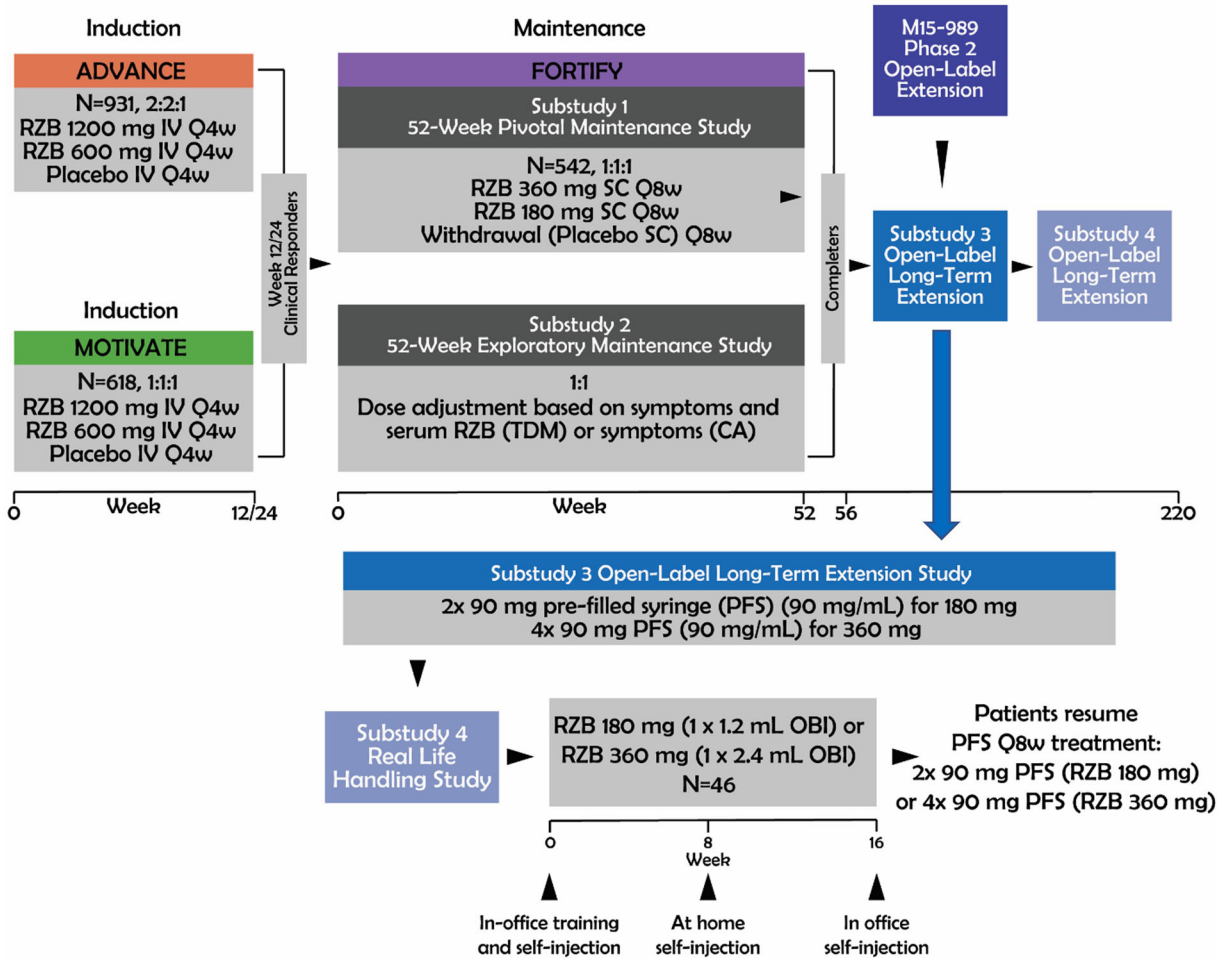

Fig. 1 FORTIFY study design

patients remained on 360 mg SC Q8w in SS3/4. Patients in SS3 self-administered risankizumab via two (180 mg) or four (360 mg) PFS (90 mg/1 mL), respectively (Fig. 1B).

SS4 enrolled a subset of patients in SS3 and consisted of a 'real-life handling study' (RLHS) period, during which the OBI usability was evaluated, and an ongoing OLE PFS period. During the RLHS period, patients received the same dose of risankizumab via OBI as they received via PFS in SS3, but one OBI (360 mg [2.4 mL, 150 mg/mL)] replaced 4 PFS for patients on 360 mg SC and one OBI [180 mg (1.2 mL, 150 mg/mL)] replaced 2 PFS for patients on 180 mg SC. The patient's ability to self-administer risankizumab via OBI was evaluated at Weeks 0, 8, and 16. At the Week 0 visit, patients were trained (pre-injection) on OBI use by site staff using the Instructions for Use (IFU; Table S1) and a training video. Patients were instructed to follow the IFU and administer risankizumab using the OBI on the abdomen or thigh. After training, site staff observed the patient self-administer risankizumab using the OBI. Site staff were instructed not to intervene with any self-administration unless the patient was going to harm themselves. The patient was then sent home with an OBI kit and the IFU with instructions to self-administer risankizumab via OBI at home at Week 8. Additional training was not provided unless requested by the patient to the site staff (i.e., the patient was to call the site for additional help if needed). At Week 16, the patient returned to the site and self-administered risankizumab using the OBI, in the healthcare provider setting in front of site staff with the IFU as reference (i.e., no further training was provided). At Week 24 (the first visit of the PFS period), patients returned to the site and transitioned back to 180 mg SC Q8w or 360 mg SC Q8w PFS (Fig. 1B).

Studies were approved by independent ethics committees or institutional review boards (IRBs) at each study site (see Table S9 for each study site/IRB). The central IRB for this study was the Advarra Central Institutional Review Board. The study conducted and reported in accordance with the protocol, and in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Adult patients and parents or legal guardians of adolescent patients provided written informed consent before screening.

Study Population

Data reported here summarize results of the SS4 RLHS period as of a data cut-off of 18 May 2022. Forty-six patients from US sites who participated in FORTIFY SS3 (37 of whom completed SS1, and 9 of whom completed SS2) participated in the RLHS portion of SS4. Eligible patients received maintenance treatment in SS3, were willing to comply with the requirements of SS4, including self-administration with the OBI, and were on stable doses of risankizumab (i.e., in SS3 for at least 16 weeks and no risankizumab rescue within 16 weeks).

Efficacy Variables

Key efficacy variables included OBI usability as determined by an observer rating of successful self-administration at Weeks 0 and 16 (defined by completing all ten critical steps of the IFU as scored by site staff) (Table S1), use-related hazard-free self-injection, and rating of patient experience using the SIAQ (Self-Injection Assessment Questionnaire) at Weeks 0, 8, and 16. The SIAQ consists of two modules: a pre-module and a post-module [11]. The pre-module was administered at baseline immediately before the initial OBI use at Week 0, and included three domains: 'feelings about injections,' 'self-confidence,' and 'satisfaction with self-injection.' The post-module was completed by the patient 20–40 min following each OBI use at Weeks 0, 8, and 16. The post-module comprised six domains: 'feelings about injections,' 'self-image,' 'self-confidence,' 'pain and skin reactions during or after the injection,' 'ease of use of the self-injection device,' and 'satisfaction with self-injection.' Each domain included several individual questions with scores ranging from 1 to 5 (or from 1 to 6) that were later transformed into scores ranging from 0 (worst experience) to 10 (best experience) (Table S2). Higher domain scores indicated

higher acceptability by patients to use the OBI. The proportion of patients in clinical remission [CD Activity Index (CDAI) < 150] at Weeks 0 and 16 was also assessed.

Pharmacokinetics and Immunogenicity

Risankizumab concentrations in human serum were measured via a ligand binding electrochemiluminescence immunoassay. Anti-drug antibodies (ADAs) in human serum were measured via a three-tiered bridging electrochemiluminescence immunoassay. A competitive ligand binding assay was used to measure neutralizing antibodies (NAbs) in human serum samples. Additional details on these bioanalytical assays can be found in a recent publication by Suleiman et al. [12].

Risankizumab serum concentrations and ADAs were evaluated prior to dosing at Weeks 0 and 16. Serum trough concentrations of risankizumab were summarized by visit and treatment arm. The incidence of risankizumab treatment-emergent ADAs during Weeks 0–16 was summarized by treatment arm. NAbs were assessed only when the ADA assessment was positive. Incidence of ADAs (treatment-emergent) to risankizumab was defined when a patient was ADA–negative or missing assessment at baseline, and became ADA-positive at one or more time points post-Week 0 visit, or ADA-positive at baseline and showed a fourfold or greater increase in titer values relative to baseline. Baseline was defined as the time prior to any risankizumab treatment (i.e., prior to induction treatment) for each individual patient.

Usability and Acceptability Experience

Usability of the OBI was assessed by an observer rating of successful, use-related hazard-free self-injection. Successful self-injection was defined as successful completion of ten critical steps within the IFU ('leaves carton at room temperature for 45 min', 'fully opens gray door', 'loads cartridge into injector', 'closes gray door', 'chooses injection area', 'peels large section using green pull tab to expose adhesive', 'peels small section using green pull tab to expose adhesive', 'places injector on skin', 'starts injection', 'waits for injection to finish') without use errors to administer the study drug, and measured at Week 0 and at Week 16 by an observer at the study site (Table S1). Possible OBI use-related hazards assessed included 'delayed administration due to device malfunction (did not wait 45 min, at room temperature)', 'administration delayed because door could not be opened or was damaged', 'administration delayed/not completed because device was damaged after drop' (and the related hazards of 'sharps exposure after the device was dropped' and 'shock after the device was dropped'), 'small component swallowed after removing the cartridge top', 'administration delayed because cartridge was not able to be inserted', 'administration delayed because adhesive liner was not removed/adhesive was removed', 'sharps exposure (e.g., needlestick)', 'injection at incorrect site', 'administration not completed because of device delivery error notification because any of the following: accidental button press, door not fully closed (no snap heard), cartridge not inserted fully (no click heard), cartridge top removed/rotated, device falls off during use', and 'underdose (e.g., wet injection, error notification, drug still visible in the medicine window)'. A device delivery error notification was communicated to the user via a red flashing light and beeping sound.

Safety

Safety evaluations for the RLHS period included data from the first dose of risankizumab administered via OBI at Week 0 until the first PFS dose at Week 24. Evaluations included adverse event (AE) monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry). Treatment-emergent AEs within the RLHS were defined as any event with an onset that was during and/or after the first dose of risankizumab via OBI, and with an onset date within 20 weeks (140 days) after the last dose of risankizumab with the OBI or the first dose of PFS, whichever occurred earlier. As part of safety

assessments, a search for hypersensitivity-related AEs was conducted using the 'Hypersensitivity' (narrow) Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query, and injection site reactions were identified using the 'Injection Site Reaction' Customized MedDRA Query.

Statistical Analysis

A sample size of approximately 50 patients was based on the assumption that the point estimate would be 90% for the proportion of subjects with an observer rating of successful subject self-administration at Week 16; this sample size was expected to provide a 95% confidence interval ± 8.3% around the point estimate.

All summary statistics for usability and efficacy were conducted in the intention-to-treat (ITT) population for SS4 (ITT4), and summary statistics for safety were conducted in the Safety Analysis population; both populations included all patients who had at least one dose of the study drug in SS4. No statistical tests were performed. Categorical variables were summarized by frequencies, percentages, and the 95% confidence intervals (CIs). Continuous variables were summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum). CDAI clinical remission was analyzed using the Non-Responder Imputation (NRI) method for missing evaluations, as well as the As-Observed (AO) method. For NRI, any patient without an evaluation during a pre-specified visit window (either due to missing assessment or due to early withdrawal from the study) was categorized as a non-responder for the visit, while values were not imputed for missing evaluations for AO. Usability endpoints were summarized using the AO method. Missing safety data were not imputed. AEs were summarized according to the MedDRA coding dictionary v.23.1. Specific AEs were counted once for each patient for calculating percentages. If the same AE occurred multiple times within a patient, the highest severity and level of relationship to investigational product was reported. Treatment-emergent AEs (TEAEs) within the RLHS were defined as events that began either on or after the first dose of the study drug via OBI in the SS4, and within 140 days after the last dose administration of the study drug via OBI or the first dose of PFS in the SS4, whichever occurred earlier.

RESULTS

FORTIFY SS4 was conducted from June 17, 2021, to May 18, 2022, at 24 sites in the US. A total of 46 patients were enrolled in the study: 31 patients in the 180 mg OBI treatment arm and 15 patients in the 360 mg OBI treatment arm. Only patients who received rescue therapy prior to SS4 entry remained on 360 mg in SS4; therefore, fewer patients were in this treatment arm due to study design.

Patient Baseline Demographics and Disease Characteristics

A similar number of males and females (Table 1) were enrolled in FORTIFY SS4 [22 females (47.8%), 24 males (52.2%)]. Of the 46 patients enrolled, 21 (45.7%) were 18 to < 40 years old, 20 (43.5%) were between the ages of ≥ 40 and < 65 years, and 5 (10.9%) were ≥ 65 years old. Similar numbers of patients had a normal (14), overweight (15), and obese (14) body mass index (BMI), with two having an underweight BMI (and one missing data at Week 0). Average daily stool frequency (SD) was 2.2 (2.3), average daily abdominal pain (SD) was 0.5 (0.5), and CDAI (SD) was 113.3 (69.9).

Patient Disposition

In total, 46, 42, and 45 patients self-administered risankizumab using the OBI at Week 0 (in office), Week 8 (at home), and Week 16 (in office), respectively (Table S3). Three patients returned unused Week 8 kits and reported missing the dose (reasons captured were travel

Table 1 Baseline demographic and disease characteristics of the ITT population

	FORTIFY SS4		
	Risankizumab 180 mg OBI ($n = 31$)	Risankizumab 360 mg OBI ($n = 15$)	All Risankizumab OBI ($n = 46$)
Completed study drug, *n* (%)	31 (100%)	15 (100%)	46 (100%)
Sex, *n* (%)			
Female	14 (45.2)	8 (53.3)	22 (47.8)
Male	17 (54.8)	7 (46.7)	24 (52.2)
Age (years), mean (SD)	43.4 (13.8)	38.1 (13.1)	41.7 (13.7)
Weight (kg), mean (SD)	88.3 (23.9)	80.0 (30.3)	85.6 (26.1)
Body mass index	29.3 (7.4)	27.6 (9.4)	28.7 (8.1)
Race—*n* (%)			
White	26 (83.9)	12 (80.0)	38 (82.6)
Black or African American	5 (16.1)	3 (20.0)	8 (17.4)
Ethnicity, *n* (%)			
Hispanic/Latino	1 (3.2)	1 (6.7)	2 (4.3)
Non-Hispanic/Latino	30 (96.8)	14 (93.3)	44 (95.7)
Biologics failure history, *n* (%)			
0	10 (32.3)	3 (20.0)	13 (28.3)
1	10 (32.3)	7 (46.7)	17 (37.0)
≥ 2	11 (35.5)	5 (33.3)	16 (34.8)
CDAI, mean (SD)	96.9 (53.3)	147.2 (88.3)	113.3 (69.9)
Average daily stool frequency, mean (SD)	1.9 (2.1)	2.8 (2.8)	2.2 (2.4)
Average daily abdominal pain score, mean (SD)	0.4 (0.5)	0.7 (0.5)	0.5 (0.5)

and feeling healthy). A fourth patient did not return a kit, and there was no confirmation of self-administration. At Week 16, 45 of 46 patients self-administered. One patient had the study drug interrupted due to a serious AE and did not self-administer with the OBI. No patient prematurely discontinued in FORTIFY SS4. Most self-administrations occurred in the abdomen, with 69.6% (32/46), 58.7%, (27/42), and 76.1% (35/45) injecting in the abdomen at Weeks 0, 8, and 16, respectively.

Successful Self-Administration

Self-administration, as observed by site staff, was assessed on a patient level at Weeks 0 and 16. At the Week 0 visit, 100% of patients (46/46) successfully self-administered risankizumab via OBI, including two patients who experienced a dosing failure (no drug administered) during their first self-administration attempt, and required a second OBI to successfully self-administer during a subsequent attempt. At Week 16, 100% of patients (44/44) successfully self-administered risankizumab via OBI, including

one patient who again experienced a dosing failure and required a second OBI to successfully self-administer risankizumab. Five use-related hazards, as described below, were assessed by site staff for the patient for whom a second OBI at both Weeks 0 and 16 was required.

Achievement of No Potential Use-Related Hazards

Overall, the proportion of patients achieving zero use-related hazards with the OBI was high [44/46 (95.7%)] at both Week 0 and Week 16 [95.5% (42/44); Table S5]: 2 patients did not complete the case report form for use-related hazards at Week 16, and therefore only 44 patients were assessed at Week 16. Use-related hazards related to dosing failure were observed for two patients at Week 0 and one patient at Week 16 (for whom use-related hazards were also reported at Week 0). An additional patient had missing values for one of the assessed use-related hazards at Week 16, and was conservatively counted as having a use-related hazard. All use-related hazards assessed are shown in Table S6. For the patient with use-related hazards assessed at both Week 0 and 16, three use-related hazards (administration delayed due to device malfunction, door could not open/was damaged, administration was not completed because of device delivery error notification) were reported for the Week 0 injection, while two use-related hazards (door could not open/was damaged, administration was not completed because of device delivery error notification) were reported for the Week 16 injection. In both instances, the patient reported that the OBI door would not close. For this patient, as well as for the other patient who required a second OBI for successful risankizumab administration at Week 0, the root cause was determined to be incomplete cartridge insertion; these patients were able to complete all critical steps of the IFU with a second OBI. A use-related hazard of underdose was assessed for the second patient at Week 0. The root cause of this dosing failure was determined to be that the start button was pressed prior to securely placing the OBI on the skin, which resulted in dampness at the injection area of the OBI (i.e., 'wet injection'). Inspection by the site staff revealed that the adhesive was not securely attached to the skin. Secure attachment led to the resolution of the damp sensation, and the device performed as intended.

Patient Rating of Acceptability

The mean (SD) SIAQ pre-dose (3 modules) domain scores were high prior to the initial administration of risankizumab via OBI ('feelings about injection,' 8.5 (2.0); 'self-confidence,' 8.5 (1.9); and 'satisfaction with self-injection,' 8.4 (1.9), indicating a positive feeling toward self-administered injections prior to OBI use. Post-dose (6 modules) domain scores were high (i.e., ≥ 8.5) after initial OBI use at Week 0 (positive feelings about self-administered injections = 9.0, self-image = 9.5, self-confidence = 8.8, pain and skin reactions during or after the injection = 9.3, ease of use of the self-injection device = 8.9, and satisfaction with self-injection = 8.5) and remained consistently high following at home injection at Week 8 and after final OBI-mediated risankizumab administration at Week 16 (Fig. 2).

The proportion of patients achieving the top two response categories in both the pre- and post-modules of the SIAQ are presented in Table S7. Results from select individual questions in the post-module provided additional context to the ease of administration, satisfaction, and self-confidence in self-administration of the OBI (Table 2). For example, in response to the question 'How difficult or easy was it to use the self-injection device?', 93.2% (41/44) of patients answered 'easy' or 'very easy' at Week 0, followed by 97.7% (43/44) at Week 16. In response to 'How difficult or easy was it to administer the injection without any help?', 90.9% (40/44) answered 'easy' or 'very easy' at Week 0, followed by 93.2% (41/44) at Week 16. In addition, 97.7% (43/44) responded that it was 'very easy' or 'extremely easy' to 'give yourself an injection' at Week 0, followed by 93.2% (41/44) at Week 16, 90.9% (40/44) were 'satisfied' or 'very satisfied' with 'your current way of taking your medication (self-injection)'

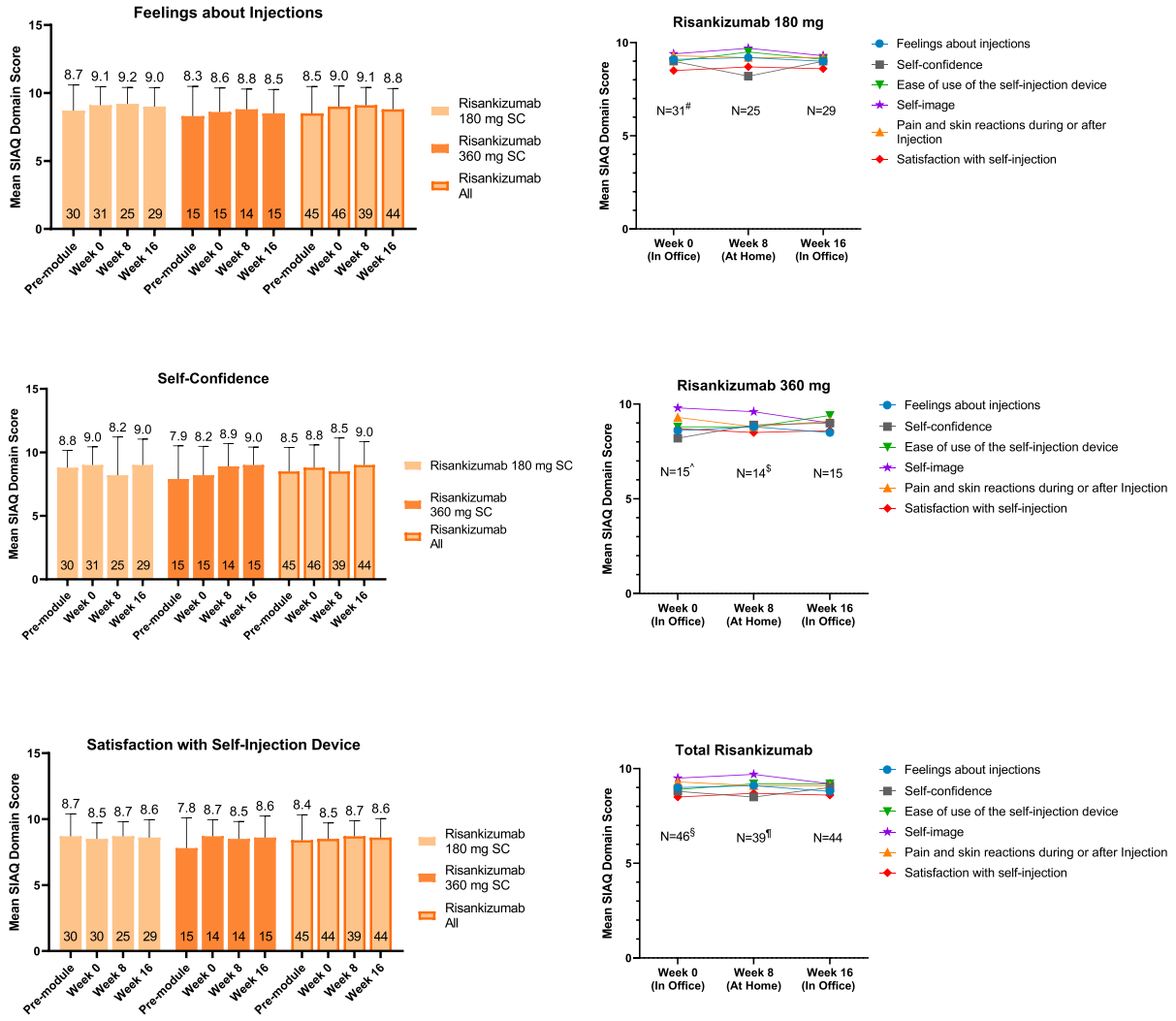

Fig. 2 Post-module mean SIAQ domain scores over time, ITT4[a], AO[b]. [a]ITT4 Population includes all patients who received at least one dose of study drug in the substudy 4; [b]Data are as observed. Scores range from 0 (worst experience) to 10 (best experience).[#] $n = 31$ except for 'Ease of use of the self-injection device' and 'Satisfaction with self-injection', $n = 30$; [^] $n = 15$ except for 'Pain and skin reactions during or after the injection,' 'Ease of use of the self-injection device,' 'Satisfaction with self-injection', $n = 14$; [$] $n = 14$ except for 'Self image,' $n = 13$; [§] $n = 46$ except for 'Pain and skin reactions during or after the injection,' $n = 45$, 'Ease of use of the self-injection device' and 'Satisfaction with self-injection,' $n = 44$; [¶] $n = 39$ except for 'Self-image,' $n = 38$

at Week 0, followed by 84.1% (37/44) at Week 16, 97.7% (43/44), were 'very' or 'extremely' confident to 'give yourself injections at home' at Week 0, followed by 95.5% (42/44) at Week 16, and 87% (40/46) were 'very confident' or 'extremely confident' in 'giving your injection in the right way' at Week 0, followed by 93.2% (41/44) at Week 16.

CDAI Clinical Remission

CDAI clinical remission (CDAI < 150) was stable over the 16-week OBI treatment period. For patients with available data (i.e., per AO analyses), 82.2% (37/45) of patients at Week 0 were in clinical remission and 84.2% (32/38) were in clinical remission at Week 16 (Fig. 3). Based on NRI analyses, 80.4% (37/46) of

Table 2 Results from selected individual questions from the SIAQ post-module for self-administration of risankizumab via an OBI at Week 0 and Week 16 (ITT4 population)

SIAQ domain	Question	Response	Post-module Week 0 *n*/*N* (%)	Post-module Week 8 *n*/*N* (%)	Post-module Week 16 *n*/*N* (%)
Ease of use of the self-injection device	How difficult or easy was it to use the self-injection device?	Easy or very easy	41/44 (93.2)	38/39 (97.4)	43/44 (97.7)
	How difficult or easy was it to administer the injection without any help?	Easy or very easy	40/44 (90.9)	38/39 (97.4)	41/44 (93.2)
Satisfaction with self-injection	How easy was it to give yourself an injection?	Very or extremely easy	43/44 (97.7)	38/39 (97.4)	41/44 (93.2)
	Overall, how satisfied are you with your current way of taking your medication (self-injection)?	Satisfied or very satisfied	40/44 (90.9)	35/39 (89.7)	37/44 (84.1)
	After this study, how confident would you be to give yourself injections at home	Very or extremely	43/44 (97.7)	38/39 (97.4)	42/44 (95.5)
Self-confidence	How confident are you about giving yourself an injection in the right way?	Very or extremely confident	40/46 (87.0)	34/39 (87.2)	41/44 (93.2)

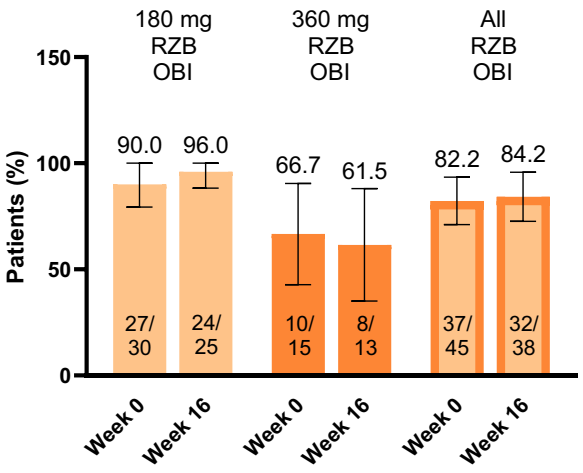

Fig. 3 CDAI clinical remission[a], ITT4[b], AO[c]. [a]CDAI clinical remission is defined as CDAI < 150; [b]ITT4 population includes all patients who received at least one dose of study drug in the substudy 4; [c]data are as observed; all available measurements were used for analysis and did not impute values for missing evaluations

subjects at Week 0 were in clinical remission and 69.6% (32/46) were in clinical remission at Week 16.

Pharmacokinetics and Immunogenicity

Following risankizumab 180 mg SC and 360 mg SC administration via OBI at Weeks 0 and 8, serum trough concentrations were consistent between Week 0 (median at 5.99 and 8.01 μg/mL for 180 and 360 mg, respectively) and Week 16 (median at 5.48 and 7.35 μg/mL for 180 and 360 mg, respectively) time points for both dose arms, with dose-related differences between 180 and 360 mg, demonstrating that doses administered via OBI achieved the expected risankizumab exposures for these patients (Fig. 4).

Overall treatment-emergent ADA and NAb incidence in patients who received either 180 or 360 mg OBI during Weeks 0–16 was 2.2% (1/46) and 0%, respectively (Table S8). Following the

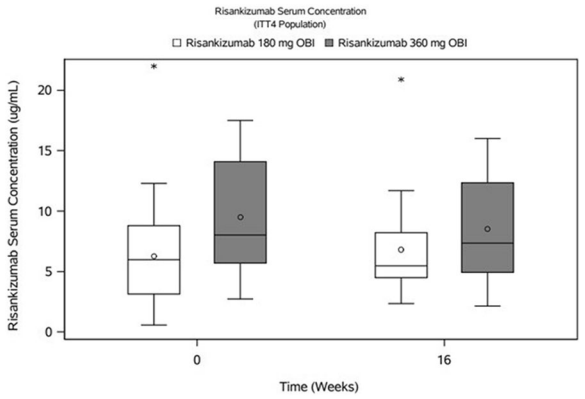

Fig. 4 Risankizumab serum trough concentration by maintenance regimen at Weeks 0 and 16 in SS4. Risankizumab concentrations at scheduled pharmacokinetic assessments in the study. Horizontal bars in each box represent median, open circles represent arithmetic mean, whiskers extending from each box represent 1.5 times the inter-quartile range (25th to 75th percentiles)

use of OBI during the study, no patient developed de novo ADAs or NAbs, indicating no marked impact on immunogenicity by SC administrations via OBI (Table S8).

Safety

TEAEs were reported in 41.3% (19/46) of patients (Table 3). Most frequently reported AEs (by MedDRA 23.1 Preferred Term) included COVID-19 [4/46 (8.7%), all in the 180-mg risankizumab OBI arm] and hypokalemia [3/46 (6.5%), all in the 180-mg risankizumab OBI arm]. No other TEAE was reported in more than two subjects.

Three patients reported a total of five serious AEs (SAEs), all in the 180 mg risankizumab OBI arm. One patient with history of stenosing ileal CD experienced two SAEs (reported terms, inflamed terminal ileum with small bowel perforation on day 97 after the baseline of SS4, and surgical removal of perforated ileal stricture on day 142 after the baseline of SS4); neither event was considered to be related to risankizumab or the OBI by the investigator. The second patient experienced an SAE of acute pancreatitis on day 138 after the baseline of SS4 that was judged not to be related to risankizumab nor the OBI by the investigator. The third patient experienced SAEs of Crohn's colitis and intestinal obstruction on day 127 after the baseline of SS4; neither event was considered related to risankizumab or the OBI by the investigator.

Two patients (4.3%, 2/46) reported non-serious AEs of hypersensitivity, both dermatitis contact, which were assessed by the investigator as related to the OBI; one event was at Week 0 (180 mg risankizumab) and was mild in severity, while the other was at Week 8 (360 mg risankizumab) and was moderate in severity. Both events resolved, and both subjects self-administered with the OBI at the subsequent visits without further hypersensitivity AEs reported. An additional patient experienced a non-serious AE of rash (papular skin rash on back), that was moderate in severity and occurred approximately 4 weeks after the Week 16 OBI administration. The event was considered not related to the OBI and was assessed as

Table 3 Overview of TEAEs

Treatment-emergent adverse events	RISA 180 mg OBI ($n = 31$) n (%)	RISA 360 mg OBI ($n = 15$) n (%)	RISA Total OBI ($n = 46$) n (%)
Adverse event (AE)	15 (48.4)	4 (26.7)	19 (41.3)
AE related to COVID-19	4 (12.9)	0	4 (8.7)
AE with reasonable possibility of being study drug related	2 (6.5)	1 (6.7)	3 (4.3)
AE related to OBI	1 (3.2)	1 (6.7)	2 (4.3)
Severe AE	2 (6.5)	0	2 (4.3)
Serious AE (SAE)	3 (9.7)	0	3 (6.5)
AE leading to discontinuation of study drug	0	0	0
Death	0	0	0

Safety assessed in all patients who received at least one dose of risankizumab

having a reasonable possibility of being related to risankizumab per investigator's opinion. There were two non-serious events of injection site reactions (180 mg risankizumab OBI). One patient reported events of injection site redness and injection site erythema (described as mild pain and discomfort that was related to the OBI adhesive pulling the hair) at the Week 0 visit. The other patient reported injection site pain at the Week 16 visit. Both events were mild, transient (resolved in 1 day), and neither was considered related to study drug or the OBI according to the investigator. No AEs were reported in other areas of safety interest.

DISCUSSION

The FORTIFY 'Real-Life Handling' SS4 was conducted to evaluate the ability of patients with CD to self-administer risankizumab in a safe and effective manner using an OBI, and to understand its generalizability to real-world performance. Assessment of patients at Week 0 captured real-world unfamiliarity related to the introduction and initiation of a new treatment using a new device, while Week 16 self-administration performance data permitted the highest fidelity approximation of real-world use, providing an unbiased assessment of performance and enabling a better understanding the risk of using the OBI for CD patients over time. At both site visits, all patients under observation successfully self-administered risankizumab via OBI, including two patients at Week 0, and one patient at Week 16, who encountered dosing failures. These patients were able to identify key notifications for dosing errors highlighted in the IFU and successfully self-administered with a second OBI. Moreover, at the Week 16 visit, all patients performed the critical tasks of OBI self-administration without further training, feedback, or intervention from site staff. There were no unanticipated clinical concerns or harm associated with the use of the OBI.

The rate of CDAI clinical remission was sustained over 16 weeks, regardless of change from PFS to OBI. The patient experience with the OBI was positive after the Week 0 self-administration, including for patients with dosing failures on the first attempt. This positive experience was maintained at the Week 8 (at home) and after the Week 16 self-administrations, as measured by the SIAQ, and included positive feelings about injections, self-image, self-confidence, pain, and skin reactions during or after the injection, ease of use of the self-injection device, and satisfaction with the injections. The mean domain scores were high throughout the study (i.e., mean scores ≥ 8.5 on a 10-point scale at every timepoint). Moreover, based on the five response categories of the SIAQ, most patients rated the OBI as 'easy' or 'very easy' to use the OBI, were 'satisfied' or 'very satisfied' with self-injection, and were 'very' or 'extremely confident' in giving themselves an injection in the right way. High domain and individual question scores were consistent with another RLHS in psoriasis patients where use of an autoinjector administering the same 150 mg/mL formulation of risankizumab was evaluated [13]. A limitation of this study is that it included a relatively modest number of patients, albeit a sufficient number to address the research question. Also, because participation in the study was voluntary, there may have been a selection bias for the patient population. Finally, while the study was designed to assess real-world performance, the simulation nature of this study may also be considered a limitation.

Risankizumab trough serum concentrations were maintained at Week 16 compared to Week 0, suggesting that the drug was successfully delivered via OBI as expected. There was no marked impact on immunogenicity;, no subjects developed de novo ADAs or NAbs following the use of OBI, and no new safety concerns were identified based on analysis of AEs and product complaints.

CONCLUSION

The efficacy, safety, and usability of 150 mg/mL risankizumab delivered via OBI support its use in patients with moderate to severe CD.

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Compliance with Ethics Guidelines. Studies were approved by independent ethics committees or institutional review boards (IRBs) at each study site (see Table S9 for each study site/IRB). The central IRB for this study was Advarra Central Institutional Review Board. The study conducted and reported in accordance with the protocol and in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Adult patients and parents or legal guardians of adolescent patients provided written informed consent before screening.

Data Availability. The datasets generated during and/or analyzed during the current study are available upon reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g. protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. 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 and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-informationsharing/data-and-information-sharing-with-qualified-researchers.html.

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