1. NAME OF THE MEDICINAL PRODUCT

Skyrizi® 600 mg
Skyrizi® 360 mg
Skyrizi® 180 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Skyrizi 600 mg- concentrate for solution for infusion

Each vial contains 600 mg of risankizumab in 10.0 mL of solution (60mg/mL).

Skyrizi 360 mg- solution for injection in cartridge

Each cartridge contains 360 mg of risankizumab in 2.4 mL solution (150 mg/mL).

Skyrizi 180 mg- solution for injection in cartridge

Each cartridge contains 180 mg of risankizumab in 1.2 mL solution (150 mg/mL).

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody produced in Chinese Hamster Ovary cells using recombinant DNA technology.

Excipients with known effect

Skyrizi 600mg

This medicinal product contains 2 mg of polysorbate 20 in each 600 mg dose and 4 mg of polysorbate 20 in each 1,200 mg dose.

Skyrizi 180mg and Skyrizi 360mg

This medicinal product contains 0.24 mg of polysorbate 20 in each 180 mg dose and 0.48 mg of polysorbate 20 in each 360 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Skyrizi 600 mg
Concentrate for solution for infusion (infusion).
The solution is colourless to slightly yellow and clear to slightly opalescent

Skyrizi 180 mg and 360 mg
Solution for injection (injection).
The solution is colourless to yellow and clear to slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Crohn’s disease

Skyrizi 360mg and 600mg are indicated for the treatment of patients 16 years and older with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy, or if such therapies are not advisable.

Ulcerative colitis
Skyrizi 180mg, 360mg and 600mg are indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

4.2 Posology and method of administration
This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Skyrizi is indicated.

Posology

Crohn’s disease

The recommended dose is 600 mg administered by intravenous infusion at week 0, week 4, and week 8, followed by 360 mg administered by subcutaneous injection at week 12, and every 8 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

Ulcerative colitis

The recommended induction dose is 1200 mg administered by intravenous infusion at week 0, week 4, and week 8. Starting at week 12 and every 8 weeks thereafter, the recommended maintenance dose is based on individual patient presentation:

- A dose of 180 mg administered by subcutaneous injection is recommended for patients with adequate improvement in disease activity after induction
- A dose of 360 mg administered by subcutaneous injection is recommended for patients with inadequate improvement in disease activity after induction

Consideration should be given to discontinuing treatment in patients who have shown no evidence of therapeutic benefit by week 24.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly

No dose adjustment is required (see section 5.2).
There is limited information in subjects aged ≥65 years.

Renal or hepatic impairment

No specific studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of Skyrizi. These conditions are generally not expected to have any

significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of Skyrizi for the treatment of Crohn's disease in children and adolescents younger than 16 years of age have not yet been established.
The safety and efficacy of Skyrizi in children aged 0-17 years for the treatment of ulcerative colitis have not yet been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on posology can be made.

Overweight patients

No dose adjustment is required (see section 5.2).

Method of administration

Skyrizi 600 mg is administered by intravenous infusion.

Skyrizi 600 mg, concentrate for solution for infusion, is for intravenous use only. The 600 mg dose should be administered over at least one hour, and the 1200 mg dose should be administered over at least two hours. For instructions on dilution of the medicinal product before administration, see section 6.6.

Skyrizi 180 mg and 360 mg are administered by subcutaneous injection.

The injection should be administered in the thigh or abdomen. Skyrizi should not be injected into areas where the skin is tender, bruised, erythematous, indurated or damaged.
Patients may self-inject Skyrizi after training in subcutaneous injection technique with the on-body injector. Patients should be instructed to read the 'Instructions for use' provided in the package leaflet before administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Risankizumab may increase the risk of infection.

In patients with a chronic infection, a history of recurrent infection, or known risk factors for infection, risankizumab should be used with caution. Treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with risankizumab should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops such an infection or is not responding to standard therapy for the infection, the patient should be closely monitored and risankizumab should not be administered until the infection resolves.

Tuberculosis

Prior to initiating treatment with risankizumab, patients should be evaluated for tuberculosis (TB) infection. Patients receiving risankizumab should be monitored for signs and symptoms of active TB. Anti-TB therapy should be considered prior to initiating risankizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Immunisations

Prior to initiating therapy with risankizumab, completion of all appropriate immunisations should be considered according to current immunisation guidelines. If a patient has received live vaccination (viral or bacterial), it is recommended to wait at least 4 weeks prior to starting treatment with risankizumab. Patients treated with risankizumab should not receive live vaccines during treatment and for at least 21 weeks after treatment (see section 5.2).

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab (see section 4.8). If a serious hypersensitivity reaction occurs, administration of risankizumab should be discontinued immediately and appropriate therapy initiated.

Excipients with known effect

Polysorbate

Skyrizi 600mg
This medicinal product contains 2 mg of polysorbate 20 in each 600 mg dose and 4 mg of polysorbate 20 in each 1,200 mg dose. Polysorbates may cause allergic reactions.

Skyrizi 180mg and 360mg
This medicinal product contains 0.24 mg of polysorbate 20 in each 180 mg dose and 0.48 mg of polysorbate 20 in each 360 mg dose. Polysorbates may cause allergic reactions.

Sodium

Skyrizi 180mg, 360mg and 600mg

This medicinal product contains less than 1 mmol sodium (23 mg) per cartridge or vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Risankizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Interactions between risankizumab and inhibitors, inducers, or substrates of medicinal product metabolising enzymes are not expected and no dose adjustment is needed (see section 5.2).

Concomitant immunosuppressive therapy

The safety and efficacy of risankizumab in combination with immunosuppressants, including biologics, have not been evaluated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 21 weeks after treatment.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of risankizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy.

Breast-feeding

It is unknown whether risankizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. A decision should be made whether to discontinue/abstain from risankizumab therapy, taking into account the benefit of breast-feeding to the child and the benefit of risankizumab therapy to the woman.

Fertility

The effect of risankizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Risankizumab has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were upper respiratory infections (15.6% in Crohn's disease and 26.2% in ulcerative colitis).

Tabulated list of adverse reactions

Adverse reactions for risankizumab from clinical studies (Table 1) are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Very common	Upper respiratory infections[a]
	Common	Tinea infections[b]
	Uncommon	Folliculitis
Immune system disorders	Rare	Anaphylactic reactions
Nervous system disorders	Common	Headache[c]
Skin and subcutaneous tissue disorders	Common	Pruritus Rash Eczema
	Uncommon	Urticaria
General disorders and administration site conditions	Common	Fatigue[d] Injection site reactions[e]

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis, laryngitis, tracheitis
[b] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, onychomycosis, tinea infection
[c] Includes: headache, tension headache, sinus headache
[d] Includes: fatigue, asthenia, malaise
[e] Includes: injection site bruising, erythema, haematoma, haemorrhage, irritation, pain, pruritus, reaction, swelling, induration, hypersensitivity, nodule, rash, urticaria, vesicles, warmth; infusion site erythema, extravasation, reaction, swelling

Description of selected adverse reactions

Psoriasis

Infections

Over the entire psoriasis programme including long-term exposure to risankizumab, the rate of infections was 75.5 events per 100 subject-years. The majority of cases were non-serious and mild to moderate in severity and did not lead to discontinuation of risankizumab. The rate of serious infections was 1.7 events per 100 subject-years (see section 4.4).

Crohn's disease
Overall, the safety profile observed in patients with Crohn's disease treated with risankizumab was consistent with the safety profile observed in patients across indications.

Infections

The rate of infections in the pooled data from the 12-week induction studies was 83.3 events per 100 subject-years in subjects treated with risankizumab 600 mg intravenously compared to 117.7 events per 100 subject-years in placebo. The rate of serious infections was 3.4 events per 100 subject-years in subjects treated with risankizumab 600 mg intravenously compared to 16.7 events per 100 subject-years in placebo (see section 4.4).

The rate of infections in the 52-week maintenance study was 57.7 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 76.0 events per 100 subject-years in subjects who received placebo after risankizumab induction. The rate of serious infections was 6.0 events per 100 subject-

years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 5.0 events per 100 subject-years in subjects who received placebo after risankizumab induction (see section 4.4).

Ulcerative colitis

Overall, the safety profile observed in patients with ulcerative colitis treated with risankizumab was consistent with the safety profile observed in patients across indications.

Infections

The rate of infections in the pooled data from the 12-week induction study was 78.3 events per 100 subject-years in subjects treated with risankizumab 1200 mg intravenously compared to 74.2 events per 100 subject-years in placebo. The rate of serious infections was 3.0 events per 100 subject-years in subjects treated with risankizumab 1200 mg intravenously compared to 5.4 events per 100 subject-years in placebo (see section 4.4).

The rate of infections in the 52-week maintenance study was 67.4 events per 100 subject-years in subjects treated with risankizumab 180 mg subcutaneously and 56.5 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 64.6 events per 100 subject-years in subjects who received placebo after risankizumab induction. The rate of serious infections was 1.1 events per 100 subject-years in subjects treated with risankizumab 180 mg subcutaneously and 0.6 events per 100 subject-years in subjects treated with risankizumab 360 mg subcutaneously after risankizumab induction compared to 2.3 events per 100 subject-years in subjects who received placebo after risankizumab induction (see section 4.4).

Immunogenicity

For subjects with Crohn's disease treated with risankizumab at the recommended intravenous induction and subcutaneous maintenance doses for up to 64 weeks in CD clinical trials, treatment-emergent anti-drug antibodies and neutralizing antibodies were detected in 3.4% (2/58) and 0% (0/58) of evaluated subjects, respectively.

For subjects with ulcerative colitis treated with risankizumab at the recommended intravenous induction and subcutaneous maintenance doses (180 mg or 360 mg) for up to 64 weeks in ulcerative colitis clinical trials, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 8.9% (8/90) and 6.7% (6/90) for the 180 mg subcutaneous dose, or 4.4% (4/91) and 2.2% (2/91) for the 360 mg subcutaneous dose, of evaluated subjects, respectively.

Antibodies to risankizumab including neutralizing antibodies were not associated with changes in clinical response or safety.

Elderly

There is limited safety information in subjects aged ≥65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC18

Mechanism of action

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Pharmacodynamic effects

In a study of subjects with psoriasis, expression of genes associated with the IL-23/IL-17 axis was decreased in the skin after single doses of risankizumab. Reductions in epidermal thickness, infiltration of inflammatory cells, and expression of psoriatic disease markers were also observed in psoriatic lesions.

In a Phase 2 study of subjects with Crohn's disease, expression of genes associated with the IL-23/Th17 axis were decreased in gut tissue after multiple doses of risankizumab. Reductions in faecal calprotectin (FCP), serum C reactive protein (CRP) and IL-22 were also observed after multiple doses in Phase 3 induction studies in Crohn's patients. Decreases in FCP, CRP and serum IL-22 were maintained out to week 52 of the maintenance study.

In a Phase 2b/3 study of subjects with ulcerative colitis, statistically significant and clinically meaningful reduction from baseline was observed in the inflammatory biomarkers, FCP and CRP, and in the IL-23 pathway-associated biomarker, serum IL-22, at week 12 of the induction study. Decreases in FCP, CRP and serum IL-22 were maintained out to week 52 of the maintenance study.

Clinical efficacy and safety

Crohn's disease

The efficacy and safety of risankizumab were assessed in 1 419 subjects with moderately to severely active Crohn's disease in three multicentre, randomised, double-blind, placebo-controlled clinical studies. Enrolled subjects were 16 years of age or older with a Crohn's Disease Activity Index (CDAI) of 220 to 450, an average daily stool frequency (SF) ≥4 and/or average daily abdominal pain score (APS) ≥2, and a Simple Endoscopic Score for CD (SES-CD) of ≥6, or ≥4 for isolated ileal disease, excluding the narrowing component and confirmed by a central reviewer.

There were two 12-week intravenous induction studies (ADVANCE and MOTIVATE), which included a 12-week extension period for subjects who did not achieve SF/APS clinical response (≥ 30% decrease in SF and/or ≥ 30% decrease in APS and both not worse than baseline) at week 12. ADVANCE and MOTIVATE were followed by a 52-week randomised withdrawal study of subcutaneous maintenance treatment (FORTIFY) that enrolled subjects with SF/APS clinical response to intravenous induction treatment, representing at least 64 weeks of therapy.

ADVANCE and MOTIVATE

In studies ADVANCE and MOTIVATE, subjects were randomised to receive risankizumab at either 600 mg (recommended dose), 1 200 mg, or placebo, at week 0, week 4, and week 8.

In ADVANCE, 58% (491/850) subjects had failed or were intolerant to treatment with one or more biologic therapies (prior biologic failure), and 42% (359/850) had failed or were intolerant to therapy with conventional therapies but not biologic therapies (without prior biologic failure). In ADVANCE, among the subjects without prior biologic failure, (87%) 314/359 were naïve to biologic therapy and the remaining 13% had received a biologic but never failed or demonstrated intolerance. All patients in MOTIVATE had prior biologic failure.

In both studies, a greater proportion of subjects treated with risankizumab achieved the co-primary endpoints of clinical remission at week 12 and endoscopic response at week 12 compared to placebo. Enhanced SF/APS clinical response and clinical remission were significant as early as week 4 in subjects treated with risankizumab and continued to improve through week 12 (Table 2).

Table 2. Efficacy results in ADVANCE and MOTIVATE

	ADVANCE			**MOTIVATE**		
	Placebo intravenously (N=175) %	**Risankizumab 600 mg intravenously (N=336) %**	**Treatment difference[d] (95% CI)**	**Placebo intravenously (N=187) %**	**Risankizumab 600 mg intravenously (N=191) %**	**Treatment difference[d] (95% CI)**
Co-primary endpoints						
Clinical remission at week 12[e]	22%	43%	22% [14%, 30%][a]	19%	35%	15% [6%, 24%][b]
Endoscopic response at week 12[f]	12%	40%	28% [21%, 35%][a]	11%	29%	18% [10%, 25%][a]
Additional endpoints						
Enhanced SF/APS clinical response at week 4[g]	31%	46%	15% [6%, 23%][b]	32%	45%	14% [4%, 23%][c]
Enhanced SF/APS clinical response at week 12[g]	42%	63%	21% [12%, 30%][a]	39%	62%	23% [13%, 33%][a]
CDAI <150 at week 4	10%	18%	8% [1%, 14%][c]	11%	21%	10% [2%, 17%][c]

CDAI <150 at week 12	25%	45%	21% [12%, 29%][a]	20%	42%	22% [13%, 31%][a]
Mucosal healing at week 12[h]	(N=173) 8%	(N=336) 21%	14% [8%, 19%][a]	(N=186) 4%	(N=190) 14%	9% [4%, 15%][b]
Endoscopic remission at week 12[i]	9%	24%	15% [9%, 21%][a]	4%	19%	15% [9%, 21%][a]

[a] Statistically significant under multiplicity-control for risankizumab vs placebo comparison ($p<0.001$).
[b] Statistically significant under multiplicity-control for risankizumab vs placebo comparison ($p\leq0.01$).
[c] Nominal $p \leq 0.05$ risankizumab vs placebo comparison.
[d] Adjusted treatment difference.
[e] Clinical remission based on SF/APS: average daily SF ≤2.8 and not worse than baseline and average daily AP score ≤1 and not worse than baseline.
[f] Endoscopic response: greater than 50% decrease in SES-CD from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease.
[g] Enhanced SF/APS clinical response: ≥60% decrease in average daily SF and/or ≥35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission.
[h] Mucosal healing: SES-CD ulcerated surface subscore of 0 in subjects with a subscore of ≥1 at Baseline.
[i] Endoscopic remission: SES-CD ≤4 and at least a 2 point reduction versus Baseline and no subscore greater than 1 in any individual variable.

At week 12, a higher proportion of subjects treated with risankizumab achieved a decrease of at least 100 points in baseline CDAI compared to placebo (ADVANCE, risankizumab =60%, placebo=37%, p<0.001; MOTIVATE, risankizumab =60%, placebo=30%, p<0.001).

At week 12, a higher proportion of subjects treated with risankizumab achieved both enhanced SF/APS clinical response and endoscopic response at week 12 compared to placebo (ADVANCE, risankizumab =31%, placebo=8%, p<0.001; MOTIVATE, risankizumab =21%, placebo=7%, p<0.001).

The results for the co-primary endpoints for the subgroups (without allowing for multiplicity) of subjects with and without prior biologic failure are presented in Table 3.

Table 3. Efficacy results at week 12 in subgroups of subjects with prior biologic treatment failure and subjects without prior biologic failure in ADVANCE

	ADVANCE		
	Placebo intravenously	**Risankizumab 600 mg**	**Treatment difference (95% CI)**
Clinical remission per SF/AP Score			
Prior biologic failure	23% (N=97)	41% (N=195)	18% [7%, 29%]
Without prior biologic failure	21% (N=78)	48% (N=141)	27% [15%, 39%]
Endoscopic response			
Prior biologic failure	11% (N=97)	33% (N=195)	21% [12%, 31%]
Without prior biologic failure	13% (N=78)	50% (N=141)	38% [27%, 49%]

In ADVANCE, a higher proportion of subjects treated with risankizumab with and without prior biologic failure achieved CDAI<150 compared to placebo (With prior biologic failure, risankizumab =42%, placebo=26%; Without prior biologic failure, risankizumab =49%, placebo=23%).

CD-related hospitalisations

Rates of CD-related hospitalisations through week 12 were lower in subjects treated with risankizumab compared to placebo (ADVANCE, risankizumab =3%, placebo=12%, p<0.001; MOTIVATE, risankizumab =3%, placebo=11%, p≤0.01).

FORTIFY

The maintenance study FORTIFY evaluated 462 subjects with SF/APS clinical response to 12 weeks of risankizumab intravenous induction treatment in studies ADVANCE and MOTIVATE. Subjects were randomised to continue to receive a maintenance regimen of risankizumab 360 mg subcutaneously (recommended dose), or risankizumab 180 mg subcutaneously every 8 weeks, or to withdraw from risankizumab induction and receive placebo subcutaneously every 8 weeks for up to 52 weeks.

The co-primary endpoints were clinical remission at week 52 and, endoscopic response at week 52. Co-primary endpoints were also measured in subjects with and without prior biologic failure (see Table 4).

Table 4. Efficacy results in FORTIFY at week 52 (64 weeks from initiation of induction dose)

	FORTIFY		
	Risankizumab intravenous induction/ Placebo subcutaneously[f] (N=164) %	**Risankizumab intravenous induction/ Risankizumab 360 mg subcutaneously (N=141) %**	**Treatment difference (95% CI)**
Co-primary endpoints			
Clinical remission	40%	52%	15% [5%, 25%][a,g]
Prior biologic failure	34% (N=123)	48% (N=102)	14% [1%,27%]
Without prior biologic failure	56% (N=41)	62% (N=39)	5% [-16%,27%]
Endoscopic response	22%	47%	28% [19%, 37%][b,g]
Prior biologic failure	20% (N=123)	44% (N=102)	23% [11%, 35%]
Without prior biologic failure	27% (N=41)	54% (N=39)	27% [6%, 48%]
Additional endpoints			
Enhanced SF/APS clinical response	49%	59%	13% [2%, 23%][e,g]
Maintenance of clinical remission[h]	(N = 91) 51%	(N = 72) 69%	21% [6%, 35%][d,g]
Endoscopic remission	13%	39%	28% [20%, 37%][c,g]
Mucosal healing	(N = 162) 10%	(N = 141) 31%	22% [14%, 30%][c,g]

[a] Statistically significant under multiplicity-control for risankizumab vs placebo comparison (p≤0.01).
[b] Statistically significant under multiplicity-control for risankizumab vs placebo comparison (p<0.001).
[c] Nominal p<0.001 risankizumab vs placebo comparison without overall type I error control.
[d] Nominal p≤0.01 risankizumab vs placebo comparison without overall type I error control.
[e] Nominal p≤0.05 risankizumab vs placebo comparison without overall type I error control.

[f] The induction-only group consisted of subjects who achieved clinical response to risankizumab induction therapy and were randomised to receive placebo in the maintenance study (FORTIFY).
[g] Adjusted treatment difference.
[h] Maintenance of clinical remission: clinical remission at week 52 in subjects with clinical remission at week 0.

Deep remission (clinical remission and endoscopic remission) at week 52 was observed at higher rates in subjects treated with risankizumab intravenously / risankizumab subcutaneously compared to subjects who received risankizumab intravenously /placebo subcutaneously (28% vs. 10%, respectively, nominal p<0.001).

At week 52, a higher proportion of subjects treated with risankizumab intravenously / risankizumab subcutaneously achieved CDAI < 150 compared to risankizumab intravenously /placebo subcutaneously (52% vs. 41%, respectively, nominal p≤0.01). A higher proportion of subjects treated with risankizumab intravenously/ risankizumab subcutaneously achieved a decrease of at least 100 points in baseline CDAI score compared to subjects treated with risankizumab intravenously /placebo subcutaneously (62% vs. 48%, respectively, nominal p≤ 0.01).

91 subjects who did not demonstrate SF/APS clinical response 12 weeks after risankizumab induction in studies ADVANCE and MOTIVATE received subcutaneous 360 mg dose of risankizumab at week 12 and week 20. Of these subjects, 64% (58/91) achieved SF/APS clinical response at week 24; 33 of the subjects achieving SF/APS clinical response enrolled in FORTIFY and continued receiving risankizumab 360 mg subcutaneously every 8 weeks for up to 52 weeks. Among these subjects, 55% (18/33) achieved clinical remission and 45% (15/33) achieved endoscopic response at week 52.

During FORTIFY, 30 subjects had loss of response to risankizumab 360 mg subcutaneously treatment and received rescue treatment with risankizumab (1 200 mg intravenous single dose, followed by 360 mg subcutaneously every 8 weeks). Of these subjects, 57% (17/30) achieved SF/APS clinical response at week 52. In addition, 20% (6/30) and 34% (10/29) of subjects achieved clinical remission and endoscopic response at week 52, respectively.

Health-related and quality of life outcomes

Health-related quality of life was assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ) and 36-Item Short Form Health Survey (SF-36). Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale. Work productivity was assessed by the Work Productivity and Activity Impairment CD (WPAI-CD) Questionnaire.

At week 12 of ADVANCE and MOTIVATE, subjects treated with risankizumab achieved clinically meaningful improvements from baseline in IBDQ total score, all IBDQ domain scores (bowel symptoms, systemic function, emotional function, and social function), SF-36 Physical and Mental Component Summary Score, FACIT-Fatigue and WPAI-CD compared to placebo. For WPAI-CD greater reductions in impairment while working, overall work impairment, and activity impairment were demonstrated in ADVANCE; and greater reduction in activity impairment was demonstrated in MOTIVATE. These improvements were maintained in subjects treated with risankizumab intravenously / risankizumab subcutaneously in FORTIFY through week 52.

Ulcerative colitis

The efficacy and safety of risankizumab was assessed in subjects with moderately to severely active ulcerative colitis in two multicentre, randomised, double-blind, placebo-controlled clinical studies. Enrolled subjects were ≥ 18 and ≤ 80 years of age with adapted Mayo Score (aMS) of 5 to 9 (using the Mayo scoring system, excluding Physician's Global Assessment) with an endoscopic subscore (ES) of 2 or 3 on screening endoscopy, confirmed by central review.

The 12-week intravenous induction study (INSPIRE) included a 12-week extension period for subjects who did not achieve clinical response [defined as a decrease from baseline in the aMS ≥ 2 points and ≥ 30% from baseline, and a decrease in rectal bleeding subscore (RBS) ≥ 1 or an absolute RBS ≤ 1] at Week 12. INSPIRE was followed by a 52-week randomised withdrawal study of subcutaneous maintenance treatment (COMMAND) that enrolled subjects with clinical response to 12 weeks of risankizumab intravenous induction treatment, representing at least 64 weeks of therapy.

INSPIRE

In study INSPIRE, 975 subjects were randomised and received either risankizumab 1 200 mg or placebo, at week 0, week 4, and week 8.

In INSPIRE, 52% (503/975) of subjects had failed (inadequate response or intolerance) one or more biologics therapies, JAK inhibitors, and/or S1P receptor modulators. Of these 503 subjects, 488 (97%) failed biologics and 90 (18%) failed JAK inhibitors.

Enrolled subjects were permitted to use a stable dose of oral corticosteroids (up to 20 mg/day prednisone or equivalent), immunomodulators, and aminosalicylates. At baseline in INSPIRE, 36% of subjects received corticosteroids, 17% of subjects received immunomodulators and 73% of subjects received aminosalicylates. Patient disease activity was moderate (aMS ≤7) in 58% of subjects and severe (aMS >7) in 42% of subjects.

In INSPIRE, a significantly greater proportion of subjects treated with risankizumab achieved the primary endpoint of clinical remission per aMS [defined as stool frequency subscore (SFS) ≤ 1, and not greater than baseline, RBS = 0, and ES ≤ 1 without evidence of friability] at week 12 compared to placebo (Table 5). Results of the primary endpoint and key secondary endpoints are listed in Table 5.

Table 5. Efficacy results in INSPIRE at week 12

Endpoint	**Placebo intravenously (N=325) %**	**Risankizumab 1 200 mg intravenously (N=650) %**	**Treatment difference (95% CI)**
Disease activity and UC symptoms			
Clinical remission[ab]	6%	20%	14%[f] [10%, 18%]
With biologic and/or JAK inhibitor failure	4% (N=170)	11% (N=333)	7% [3%, 12%]
Without biologic and/or JAK inhibitor failure	8% (N=155)	30% (N=317)	21% [15%, 28%]
Clinical response[c]	36%	64%	29%[f] [22%, 35%]
With biologic and/or JAK inhibitor failure	31% (N=170)	55% (N=333)	24% [15%, 33%]

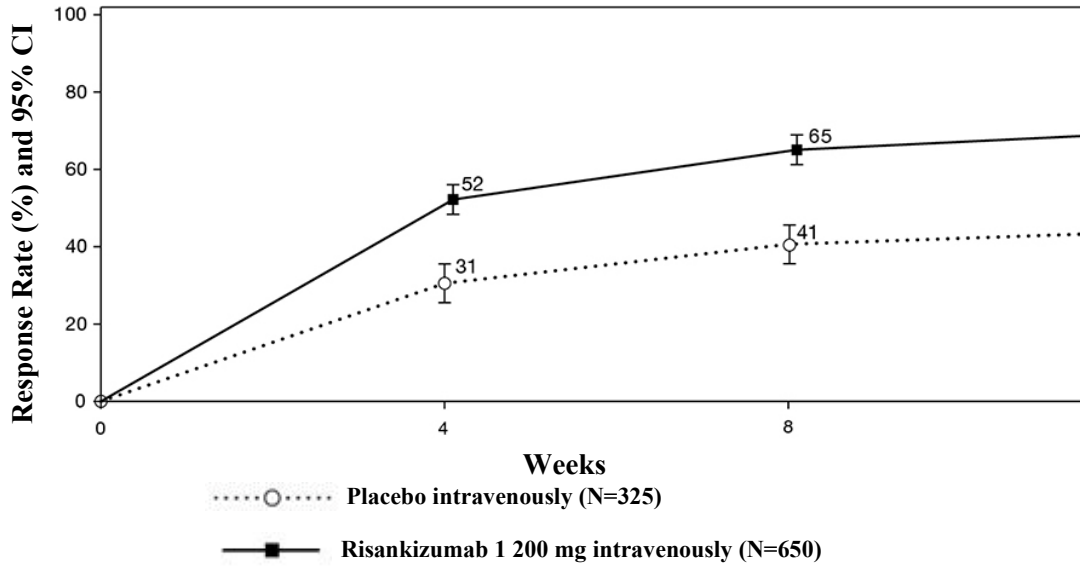
Without biologic and/or JAK inhibitor failure	41% (N=155)	74% (N=317)	33% [24%, 42%]
Endoscopic and histologic assessment			
Mucosal healing[d]	12%	37%	24%[f] [19%, 29%]
With biologic and/or JAK inhibitor failure	10% (N=170)	26% (N=333)	16% [9%, 22%]
Without biologic and/or JAK inhibitor failure	14% (N=155)	48% (N=317)	33% [26%, 41%]
Histologic-endoscopic mucosal healing[e]	8%	24%	17%[f] [12%, 21%]
With biologic and/or JAK inhibitor failure	7% (N=170)	16% (N=333)	9% [3%, 14%]
Without biologic and/or JAK inhibitor failure	8% (N=155)	33% (N=317)	25% [18%, 32%]

[a] Primary endpoint
[b] Clinical remission per aMS: SFS ≤ 1, and not greater than baseline, RBS = 0, and ES ≤ 1 without evidence of friability
[c] Clinical response per aMS: decrease from Baseline ≥ 2 points and ≥ 30%, and a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
[d] ES ≤ 1 without the evidence of friability
[e] ES ≤ 1 without the evidence of friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)
[f] $p < 0.00001$, adjusted treatment difference (95% CI)

Clinical disease activity and symptoms

The partial adapted Mayo score (paMS) is composed of SFS and RBS. Clinical response per paMS is defined as a decrease of ≥1 point and ≥30% from Baseline and a decrease in RBS ≥1 or an absolute RBS ≤1. The results of clinical response per paMS over time in INSPIRE are shown in Figure 1. Onset of efficacy was rapid with a greater proportion of subjects treated with risankizumab achieving clinical response as early as week 4 compared to placebo (52% vs 31%, respectively, $p < 0.00001$).

Figure 1. Proportion of subjects achieving clinical response per paMS over time in induction study INSPIRE



A significantly greater proportion of subjects treated with risankizumab compared to placebo had no abdominal pain (36% vs 26%, respectively, $p < 0.01$) and no bowel urgency (44% vs 28%, respectively, $p < 0.00001$) at week 12.

Other UC symptoms

Number of faecal incontinence episodes per week was reduced in a significantly greater amount in subjects treated with risankizumab compared to placebo at week 12 (change from baseline in risankizumab = -3.8, placebo = -2.2, $p = 0.00003$).

The proportion of subjects who had no nocturnal bowel movements was significantly greater in subjects treated with risankizumab compared to placebo at week 12 (67% vs 43%, respectively, $p < 0.00001$).

The proportion of subjects who had no tenesmus was significantly greater in subjects treated with risankizumab compared to placebo at week 12 (49% vs 30%, respectively, $p < 0.00001$).

Number of days with sleep interruption due to UC symptoms per week were reduced in a significantly greater amount in subjects treated with risankizumab compared to placebo at week 12 (change from baseline in risankizumab = -2.5, placebo = -1.5, $p < 0.00001$).

UC-related hospitalisations

Rates of UC-related hospitalisations through week 12 were significantly lower in subjects treated with risankizumab compared to placebo (1% vs 6%, respectively, $p < 0.00001$).

Extended treatment in week 12 non-responders

A total of 141 subjects who did not demonstrate clinical response at week 12 of risankizumab induction in INSPIRE received either subcutaneous 180 mg or 360 mg dose of risankizumab at week 12 and week 20. Of the 71 subjects who received risankizumab 180 mg subcutaneously and 70 subjects who received risankizumab 360 mg subcutaneously, 56% and 57% achieved clinical response at week 24, respectively.

COMMAND

The maintenance study COMMAND evaluated 548 subjects with clinical response after 12 weeks of risankizumab intravenous induction treatment in study INSPIRE. Subjects were randomised to receive a maintenance regimen of risankizumab 180 mg subcutaneously or 360 mg subcutaneously every 8 weeks, or to withdraw from risankizumab induction and receive placebo subcutaneously every 8 weeks for up to 52 weeks.

In COMMAND, 75% (411/548) of subjects had failed (inadequate response or intolerance) one or more biologics therapies, JAK inhibitors, and/or S1P receptor modulators prior to induction baseline. Of these 411 subjects, 407 (99%) failed biologics and 78 (19%) failed JAK inhibitors.

In COMMAND, a significantly greater proportion of the above 548 subjects treated with risankizumab 180 mg subcutaneously or risankizumab 360 mg subcutaneously achieved the primary endpoint of clinical remission per aMS at week 52 compared to placebo (see Table 6). Results of the primary endpoint and key secondary endpoints are listed in Table 6.

Table 6. Efficacy results in COMMAND at week 52 (64 weeks from initiation of induction dose)

Endpoint	Risankizumab intravenous induction/ Placebo subcutaneously[+] (N=183) %	Risankizumab intravenous induction/ Risankizumab 180 mg subcutaneously (N=179) %	Risankizumab intravenous induction/ Risankizumab 360 mg subcutaneously (N=186) %	Treatment difference (97.5% CI)[++]	
				Risankizumab intravenous induction/ Risankizumab 180 mg subcutaneously	Risankizumab intravenous induction/ Risankizumab 360 mg subcutaneously
Disease activity and UC symptoms					
Clinical remission[ab]	25%	40%	38%	16%[h] [6%, 27%]	14%[h] [4%, 24%]
With biologic and/or JAK inhibitor failure	23% (N=138)	37% (N=134)	29% (N=139)	13% [1%, 26%]	6% [-6%, 18%]
Without biologic and/or JAK inhibitor failure	31% (N=45)	51% (N=45)	62% (N=47)	20% [-3%, 43%]	31% [8%, 53%]
Maintenance of clinical remission[c]	40% (N=53)	70% (N=44)	50% (N=40)	29%[h] [7%, 51%]	13%[k] [-11%, 36%]
With biologic and/or JAK inhibitor failure	37% (N=35)	65% (N=26)	44% (N=25)	28% [0%, 56%]	7% [-22%, 36%]
Without biologic and/or JAK inhibitor failure	44% (N=18)	77% (N=18)	60% (N=15)	33% [-2%, 67%]	16% [-23%, 54%]
Corticosteroid-free clinical remission[d]	25%	40%	37%	16%[h] [6%, 26%]	14%[h] [3%, 24%]
With biologic and/or JAK inhibitor failure	23% (N=138)	36% (N=134)	29% (N=139)	13% [0%, 25%]	6% [-6%, 18%]
Without biologic and/or JAK inhibitor failure	31% (N=45)	51% (N=45)	60% (N=47)	20% [-3%, 43%]	28% [6%, 51%]
Clinical response[e]	52%	68%	62%	17%[i] [6%, 28%]	11%[j] [0%, 23%]
With biologic and/or JAK inhibitor failure	46% (N=138)	63% (N=134)	57% (N=139)	18% [4%, 31%]	11% [-2%, 25%]
Without biologic and/or JAK inhibitor failure	71% (N=45)	82% (N=45)	79% (N=47)	11% [-9%, 31%]	8% [-13%, 28%]
Endoscopic and histologic assessment					
Mucosal healing[f]	32%	51%	48%	20%[h] [9%, 31%]	17%[h] [7%, 28%]
With biologic and/or JAK inhibitor failure	30% (N=138)	48% (N=134)	39% (N=139)	17% [4%, 30%]	8% [-4%, 21%]
Without biologic and/or JAK inhibitor failure	36% (N=45)	60% (N=45)	76% (N=47)	24% [1%, 47%]	41% [19%, 62%]
Histologic-endoscopic mucosal healing[g]	23%	43%	42%	20%[h] [10%, 31%]	20%[h] [10%, 30%]
With biologic and/or JAK inhibitor failure	22% (N=138)	39% (N=134)	33% (N=139)	17% [5%, 29%]	11% [-1%, 23%]

Without biologic and/or JAK inhibitor failure	29% (N=45)	55% (N=45)	69% (N=47)	26% [3%, 49%]	40% [19%, 62%]

[+] The induction-only group consisted of subjects who achieved clinical response to risankizumab induction therapy and were randomised to receive placebo in the maintenance study (COMMAND).
[++] Adjusted difference for the overall treatment difference.
[a] Primary endpoint
[b] Clinical remission per aMS: SFS ≤ 1, and not greater than baseline, RBS = 0, and ES ≤ 1 without evidence of friability
[c] Clinical remission per aMS at week 52 among subjects who achieved clinical remission at the end of induction treatment
[d] Clinical remission per aMS at week 52 and corticosteroid-free for ≥90 days
[e] Clinical response per aMS: decrease from Baseline ≥ 2 points and ≥ 30%, and a decrease in RBS ≥ 1 or an absolute RBS ≤ 1
[f] ES of ≤ 1 without the evidence of friability
[g] ES ≤ 1 without the evidence of friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction and no erosions, ulcerations or granulation tissue)
[h] Statistically significant under multiplicity-control for risankizumab vs placebo comparison ($p \leq 0.01$).
[i] Nominal $p \leq 0.01$ risankizumab vs placebo comparison
[j] Nominal $p \leq 0.05$ risankizumab vs placebo comparison
[k] $p = 0.2234$

Clinical disease activity and symptoms

A significantly greater proportion of subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously compared to risankizumab intravenously/placebo had no abdominal pain (47% vs 30%, respectively, $p < 0.001$) and no bowel urgency (54% vs 31%, respectively, $p < 0.00001$) at week 52. A greater proportion of subjects treated with risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo had no bowel urgency (49% vs 31%, respectively, $p < 0.001$) at week 52, and a numerically higher proportion of subjects had no abdominal pain compared to risankizumab intravenously/placebo (38% vs 30%, respectively, $p = 0.0895$) at week 52.

Other UC symptoms

The proportion of subjects who had no nocturnal bowel movements was greater in subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo at week 52 (42% and 43% vs 30%, $p < 0.01$ and $p < 0.001$, respectively).

The proportion of subjects who had no tenesmus was greater in subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo at week 52 (37% and 37% vs 23%, respectively, $p < 0.01$).

UC-related hospitalisations

Occurrence of UC-related hospitalisations through week 52 were numerically lower in subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab

intravenously/placebo (0.6 per 100 subject-years and 1.2 per 100 subject-years vs 3.1 per 100 subject-years, p = 0.0949 and p = 0.2531, respectively).

Endoscopic and histologic assessment

Endoscopic remission (normalisation of the endoscopic appearance of the mucosa) was defined as ES of 0. At week 12 of INSPIRE, a significantly greater proportion of subjects treated with risankizumab compared to placebo achieved endoscopic remission (11% vs 3%, respectively, p < 0.00001). At week 52 of COMMAND, a significantly greater proportion of subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo achieved endoscopic remission (23% and 24% vs 15%, respectively, p < 0.05).

Deep mucosal healing was defined as ES of 0 and Geboes score < 2.0 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations or granulation tissue). At week 12 of INSPIRE, a significantly greater proportion of subjects treated with risankizumab compared to placebo achieved deep mucosal healing (6% vs 1%, respectively, p < 0.00001). At week 52 of COMMAND, a numerically higher proportion of subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo achieved deep mucosal healing (13% and 16% vs 10%, p = 0.2062 and p = 0.0618, respectively).

In COMMAND, maintenance of mucosal healing at week 52 (ES ≤1 without friability) was seen in a greater proportion of subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously and risankizumab intravenously/risankizumab 360 mg subcutaneously compared to risankizumab intravenously/placebo among subjects who achieved mucosal healing at the end of induction (74% and 54% vs 47%, p < 0.01 and p = 0.5629, respectively).

Rescue treatment

During COMMAND, subjects who had loss of response to risankizumab subcutaneous treatment received rescue treatment with risankizumab (a single intravenous induction dose, followed by 360 mg subcutaneously every 8 weeks). Among these subjects, in the risankizumab 180 mg subcutaneously and risankizumab 360 mg subcutaneously treatment group, 85% (17/20) and 74% (26/35) achieved clinical response at week 52, respectively. In addition, 24% (6/25) and 35% (13/37) of subjects achieved clinical remission per aMS, and 38% (10/26) and 45% (17/38) of subjects achieved endoscopic improvement at week 52 in the risankizumab 180 mg subcutaneously and risankizumab 360 mg subcutaneously treatment group, respectively.

Week 24 responders

A total of 100 subjects did not demonstrate clinical response after 12 weeks of induction treatment, received either subcutaneous 180 mg (N=56) or 360 mg (N=44) dose of risankizumab at week 12 and week 20, demonstrated clinical response at week 24, and continued receiving risankizumab 180 mg or 360 mg subcutaneously every 8 weeks for up to 52 weeks in COMMAND. Among these subjects, 46% and 45% achieved clinical response per aMS at week 52, and 18% and 23% achieved clinical remission per aMS at week 52, for risankizumab 180 mg and 360 mg subcutaneously respectively.

Health-related and quality of life outcomes

Subjects treated with risankizumab achieved clinically meaningful improvements from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) (bowel symptoms, systemic function, emotional function, and social function) compared to placebo. Changes from baseline in IBDQ total score at week 12 with risankizumab compared to placebo were 42.6 and 24.3, respectively. Changes from baseline in IBDQ total score at week 52 were 52.6, 50.3 and 35.0 in subjects treated with risankizumab intravenous/risankizumab 180 mg subcutaneously, risankizumab intravenous/risankizumab 360 mg subcutaneously and risankizumab intravenous/placebo, respectively.

Subjects receiving risankizumab experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score at week 12 compared to placebo. Changes from baseline in FACIT-F score at week 12 with risankizumab compared to placebo were 7.9 and 3.3, respectively. Changes from baseline in FACIT-F score at week 52 were 10.9, 10.3 and 7.0 in subjects treated with risankizumab intravenously/risankizumab 180 mg subcutaneously, risankizumab intravenously/risankizumab 360 mg subcutaneously and risankizumab intravenously/placebo, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetics of risankizumab was similar between plaque psoriasis and psoriatic arthritis, and between Crohn's disease and ulcerative colitis.

Absorption

Risankizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure across dose ranges of 18 to 360 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1 800 mg and 0.01 to 5 mg/kg administered intravenously.

Following subcutaneous dosing of risankizumab, peak plasma concentrations were achieved between 3-14 days after dosing with an estimated absolute bioavailability of 74-89%. With dosing of 150 mg at week 0, week 4 and every 12 weeks thereafter, estimated steady-state peak and trough plasma concentrations are 12 and 2 µg/mL, respectively.

In subjects with Crohn's disease treated with 600 mg intravenous induction dose at weeks 0, 4, and 8 followed by 360 mg subcutaneous maintenance dose at week 12 and every 8 weeks thereafter, maximum median peak and trough concentrations are estimated to be 156 and 38.8 µg/mL respectively during the induction period (weeks 8-12) and steady-state median peak and trough concentrations are estimated to be 28.0 and 8.13 µg/mL respectively during the maintenance period (weeks 40-48).

In subjects with ulcerative colitis treated with 1200 mg intravenous induction dose at weeks 0, 4, and 8 followed by 180 mg or 360 mg subcutaneous maintenance dose at week 12 and every 8 weeks thereafter, maximum median peak and trough concentrations are estimated to be 350 and 87.7 µg/mL respectively during the induction period (weeks 8-12) and steady-state median peak and trough concentrations are estimated to be 19.6 and 4.64 µg/mL for the 180 mg subcutaneous dose and 39.2 and 9.29 µg/mL for the 360 mg subcutaneous dose, respectively, during the maintenance period (weeks 40-48).

Distribution

The mean (±standard deviation) steady-state volume of distribution (V_{ss}) of risankizumab was 11.4 (±2.7) L in Phase 3 studies in subjects with psoriasis, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces. In a typical 70 kg subject with Crohn's disease, V_{ss} was 7.68 L.

Biotransformation

Therapeutic IgG monoclonal antibodies are typically degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Risankizumab is not expected to be metabolised by cytochrome P450 enzymes.

Elimination

The mean (±standard deviation) systemic clearance (CL) of risankizumab was 0.3 (±0.1) L/day in Phase 3 studies in subjects with psoriasis. The mean terminal elimination half-life of risankizumab ranged from 28 to 29 days in Phase 3 studies in subjects with psoriasis. For a typical 70 kg subject with Crohn's disease, CL was 0.30 L/day and terminal elimination half-life was 21 days.

As an IgG1 monoclonal antibody, risankizumab is not expected to be filtered by glomerular filtration in the kidneys or to be excreted as an intact molecule in the urine.

Linearity/non-linearity

Risankizumab exhibited linear pharmacokinetics with approximately dose-proportional increases in systemic exposure (C_{max} and AUC) in the evaluated dose ranges of 18 to 360 mg or 0.25 to 1 mg/kg subcutaneous administration and 200 to 1800 mg and 0.01 to 5 mg/kg administered intravenously in healthy subjects or subjects with psoriasis, Crohn's disease or ulcerative colitis.

Interactions
Interaction studies were conducted in subjects with plaque psoriasis, Crohn's disease, or ulcerative colitis to assess the effect of repeated administration of risankizumab on the pharmacokinetics of cytochrome P450 (CYP) sensitive probe substrates. The exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate) and midazolam (CYP3A substrate) following risankizumab treatment were comparable to their exposures prior to risankizumab treatment, indicating no clinically meaningful interactions through these enzymes.

Population pharmacokinetic analyses indicated that risankizumab exposure was not impacted by concomitant medicinal products used by some subjects with plaque psoriasis during the clinical studies. Similar lack of impact by concomitant medicinal products was observed based on population pharmacokinetic analyses in Crohn's disease or ulcerative colitis.

Special populations

Paediatric population

The pharmacokinetics of risankizumab in paediatric subjects under 16 years of age has not been established. Of the 1574 subjects with Crohn's disease exposed to risankizumab, 12 were 16 to 17 years old. Risankizumab exposures in 16 to 17 year-old subjects with Crohn's disease were similar to those in adults. Age was not found to have any significant impact on risankizumab exposures based on the population pharmacokinetic analyses.

Elderly

Of the 2234 subjects with plaque psoriasis exposed to risankizumab, 243 were 65 years or older and 24 subjects were 75 years or older. Of the 1574 subjects with Crohn's disease exposed to risankizumab, 72 were 65 years or older and 5 subjects were 75 years or older. Of the 1512 subjects with ulcerative colitis exposed to risankizumab, 103 were 65 years or older

and 8 subjects were 75 years or older. No overall differences in risankizumab exposure were observed between older and younger subjects who received risankizumab.

Patients with renal or hepatic impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab. Based on population pharmacokinetic analyses, serum creatinine levels, creatinine clearance, or hepatic function markers (ALT/AST/bilirubin) did not have a meaningful impact on risankizumab clearance in subjects with psoriasis, Crohn's disease, or ulcerative colitis.

As an IgG1 monoclonal antibody, risankizumab is mainly eliminated via intracellular catabolism and is not expected to undergo metabolism via hepatic cytochrome P450 enzymes or renal elimination.

Body weight

Risankizumab clearance and volume of distribution increase as body weight increases which may result in reduced efficacy in subjects with high body weight (>130 kg). However, this observation is based on a limited number of subjects with plaque psoriasis. Body weight had no clinically meaningful impact on risankizumab exposure or efficacy in psoriatic arthritis, Crohn's disease, or ulcerative colitis. No dose adjustment based on body weight is currently recommended.

Gender or race

The clearance of risankizumab was not significantly influenced by gender or race in adult subjects with plaque psoriasis, Crohn's disease or ulcerative colitis. No clinically meaningful differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in clinical pharmacokinetic studies in healthy volunteers.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on repeat-dose toxicity studies including safety pharmacology evaluations and an enhanced pre- and post- natal developmental toxicity study in cynomolgus monkeys at doses of up to 50 mg/kg/week, producing exposures 10 times the clinical exposures during induction at a dose of 600 mg intravenous every 4 weeks and 39 times the clinical exposures for maintenance when given 360 mg subcutaneously every 8 weeks for Crohn's disease. For ulcerative colitis, exposures were 5 times the clinical exposures during induction at a dose of 1200 mg intravenously every 4 weeks and 65 or 32 times the clinical exposures for maintenance when given 180 or 360 mg subcutaneously every 8 weeks.

Mutagenicity and carcinogenicity studies have not been conducted with risankizumab. In a 26-week chronic toxicology study in cynomolgus monkeys at doses of up to 50 mg/kg/week (7 times the clinical exposures during induction at a dose of 600 mg intravenous every 4 weeks and 28 times the clinical exposures for maintenance when given 360 mg subcutaneously every 8 weeks for Crohn's disease and 3 times the clinical exposures during induction at a dose of 1200 mg intravenously every 4 weeks and 45 or 23 times the clinical exposures for maintenance when given 180 or 360 mg subcutaneously every 8 weeks for ulcerative colitis), there were no pre-neoplastic or neoplastic lesions observed and no adverse immunotoxicity or cardiovascular effects were noted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium acetate trihydrate
Polysorbate 20
Acetic acid glacial
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Skyrizi 600mg
The expiry date of the product is indicated on the packaging materials.

Diluted solution for intravenous infusion

Chemical and physical in-use stability has been demonstrated for 20 hours at 2°C to 8°C (protected from light) or up to 8 hours at room temperature (protected from sunlight). Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 8 hours after dilution in the infusion bag. Exposure to indoor light is acceptable during room temperature storage and administration.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and should not be longer than 20 hours at 2°C to 8°C.

Do not freeze.

Skyrizi 360 mg
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Skyrizi 600 mg

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3

Skyrizi 180 mg and 360 mg

Store in a refrigerator (2°C - 8°C). Do not freeze.
The cartridge may be stored out of the refrigerator (up to a maximum of 25°C) for up to 24 hours.

Keep the cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

Skyrizi 600 mg

10.0 mL concentrate solution for infusion in a glass vial closed with a coated bromobutyl rubber stopper.

Skyrizi is available in packs containing 1 vial pack.

Skyrizi 360 mg

A 360 mg solution in a single use cartridge made with cyclic olefin resin with coated chlorobutyl rubber septum and coated chlorobutyl rubber piston as product-contact materials, and a resin cap. The cartridge assembly is co-packed with an on-body injector (administration device). The fluid path within the on-body injector contains polyvinyl chloride tubing and a stainless steel 29-gauge needle. The on-body injector contains silver oxide-zinc batteries and an adhesive skin patch made from polyester with an acrylic adhesive. The administration device is designed for use with the provided 360 mg cartridge.

Skyrizi 360 mg is available in packs containing 1 cartridge and 1 on-body injector.

Skyrizi 180 mg

A 180 mg solution in a single use cartridge made with cyclic olefin resin with coated chlorobutyl rubber septum and coated chlorobutyl rubber piston as product-contact materials, and a resin cap. The cartridge assembly is co-packed with an on-body injector (administration device). The fluid path within the on-body injector contains polyvinyl chloride tubing and a stainless steel 29-gauge needle. The on-body injector contains silver oxide-zinc batteries and an adhesive skin patch made from polyester with an acrylic adhesive. The administration device is designed for use with the provided 180 mg cartridge.

Skyrizi 180 mg is available in packs containing 1 cartridge and 1 on-body injector.

6.6 Special precautions for disposal and other handling

Skyrizi 600 mg

The solutions should be visually inspected for particulate matter or discoloration prior to administration. The solution should be colourless to slightly yellow and clear to slightly opalescent. The liquid may contain tiny white or clear particles. The medicinal product and its dilutions should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Instructions for dilution

This medicinal product should be prepared by a healthcare professional using aseptic technique. It must be diluted before administration.

The solution for infusion is prepared by dilution of the concentrate into an intravenous infusion bag or glass bottle containing 5% dextrose in water (D5W) or sodium chloride 9 mg/mL (0.9%) solution for infusion to a final concentration of approximately 1.2 mg/mL to 6 mg/mL. Refer to table below for dilution instructions based on patient's indication.

Indication	Intravenous induction dose	Number of 600 mg/ 10 mL vials	Total volume of 5% dextrose or sodium chloride 9 mg/mL (0.9%) solution for infusion
Crohn's disease	600 mg	1	100 mL, or 250 mL, or 500 mL
Ulcerative colitis	1200 mg	2	250 mL, or 500 mL

Prior to the start of the intravenous infusion, the content of the intravenous infusion bag or glass bottle should be at room temperature.

Infuse the diluted solution over a period of at least one hour for the 600 mg dose; at least two hours for the 1200 mg dose.
The solution in the vial and the dilutions should not be shaken.
Each vial is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Skyrizi 180 mg and 360 mg

Before injecting, the carton should be removed from the refrigerator and allowed to reach room temperature, out of direct sunlight, for 45 to 90 minutes without removing the cartridge from the carton.

Prior to use, a visual inspection of the cartridge is recommended. The solution is free from foreign particles and practically free from product-related particles. Skyrizi should not be used if the solution is cloudy or discoloured, or contains large particles. Do not shake the cartridge.

The solution should be colourless to yellow and clear to slightly opalescent.

Comprehensive instructions for use are provided in the package leaflet.

Each on-body injector with cartridge is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

AbbVie Inc., 1N Waukegan Road, North Chicago, IL 60064, USA

8. LICENSE HOLDER

AbbVie biopharmaceuticals LTD., 4 Haharash., Hod Hasharon, Israel.

9. REGISTRATION NUMBERS

Skyrizi 600mg: 172-10-37478
Skyrizi 360mg: 172-09-37477
Skyrizi 180mg: 179-61-38222

Revised in November 2025.