SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Litfulo 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ritlecitinib tosylate equivalent to 50 mg ritlecitinib.

Excipient(s) with known effect

Each hard capsule contains 21.27 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

Opaque hard capsules, yellow body and blue cap approximately 16 mm long and 6 mm wide, of which the body is printed with “RCB 50” and the cap is printed with “Pfizer” in black.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of alopecia areata.

Posology

The recommended dose is 50 mg once daily.

The benefit-risk of treatment should be re-assessed at regular intervals on an individual basis.

Consideration should be given to discontinuing patients who show no evidence of therapeutic benefit after 36 weeks.

Laboratory monitoring

Table 1. Laboratory measures and monitoring guidance

Laboratory measures	**Monitoring guidance**	**Action**
Platelet count	Before treatment initiation, 4 weeks after initiation, and thereafter according to routine patient management.	Treatment should be discontinued if platelet count is $< 50 \times 10^3/mm^3$.
Lymphocytes		Treatment should be interrupted if ALC is $< 0.5 \times 10^3/mm^3$ and may be restarted once ALC return above this value.

Abbreviation: ALC = absolute lymphocyte count

Treatment initiation
Treatment with ritlecitinib should not be initiated in patients with an absolute lymphocyte count (ALC) $< 0.5 \times 10^3/mm^3$ or a platelet count $< 100 \times 10^3/mm^3$ (see section 4.4).

Treatment interruption or discontinuation
If a patient develops a serious infection or opportunistic infection, ritlecitinib should be interrupted until the infection is controlled (see section 4.4).

Interruption or discontinuation of treatment may be needed for management of haematologic abnormalities as described in Table 1.

If treatment interruption is needed, the risk of significant loss of regrown scalp hair after a temporary treatment interruption for less than 6 weeks is low.

Missed doses
If a dose is missed, patients should be advised to take the dose as soon as possible unless it is less than 8 hours before the next dose, in which case the patient should not take the missed dose. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Renal impairment
No dose adjustment is required in patients with mild, moderate, or severe renal impairment (see section 5.2).

Ritlecitinib has not been studied in patients with end-stage renal disease (ESRD) or in patients with renal transplants and is therefore not recommended for use in these patients.

Hepatic impairment
No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see section 5.2). Ritlecitinib is contraindicated in patients with severe (Child Pugh C) hepatic impairment (see section 4.3).

Elderly
No dose adjustment is required for patients ≥ 65 years of age. There are limited data in patients ≥ 65 years of age.

Paediatric population
No dose adjustment is required for adolescents 12 to < 18 years of age.

The safety and efficacy of Litfulo in children under 12 years of age have not yet been established. No data are available.

Method of administration

Oral use.

Litfulo is to be taken once daily with or without food.

Capsules should be swallowed whole and should not be crushed, split or chewed, because these methods of administration have not been studied in clinical trials.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Active serious infections, including tuberculosis (TB) (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Ritlecitinib should only be used if no suitable treatment alternatives are available in patients:
- 65 years of age and older;
- patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
- patients with malignancy risk factors (e.g., current malignancy or history of malignancy)

Serious infections

Serious infections have been reported in patients receiving ritlecitinib. The most frequent serious infections have been appendicitis, COVID-19 infection (including pneumonia), and sepsis. Treatment with ritlecitinib must not be initiated in patients with an active, serious infection (see section 4.3).

The risks and benefits of treatment should be considered in patients:
- with chronic or recurrent infection
- who have been exposed to tuberculosis (TB)
- with a history of serious or an opportunistic infection
- who have resided or traveled in areas of endemic TB or mycoses, or
- with underlying conditions that may predispose them to infection

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ritlecitinib. Treatment should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with ritlecitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. If interrupted, ritlecitinib may be resumed once the infection is controlled.

As there is a higher incidence of infections in elderly and in the diabetic population in general, caution should be exercised when treating the elderly and patients with diabetes, and particular attention paid with respect to occurrence of infections. In patients 65 years of age and older, ritlecitinib should only be used if no suitable treatment alternatives are available (see section 4.2).

Tuberculosis
Patients should be screened for TB before starting therapy with ritlecitinib. Ritlecitinib must not be given to patients with active TB (see section 4.3). Anti-TB therapy should be started prior to initiating therapy with ritlecitinib in patients with a new diagnosis of latent TB or previously untreated latent TB. In patients with a negative latent TB test, anti-TB therapy should still be considered before initiating treatment with ritlecitinib in those at high risk and screening for patients at high risk for TB during treatment with ritlecitinib should be considered.

Viral reactivation
Viral reactivations, including cases of herpes virus reactivation (e.g., herpes zoster), have been reported (see section 4.8). If a patient develops herpes zoster, temporary interruption of treatment may be considered until the episode resolves.

Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with ritlecitinib. Patients with evidence of hepatitis B or C infection were excluded from studies with ritlecitinib. Monitoring for reactivation of viral hepatitis according to clinical guidelines is recommended during ritlecitinib treatment. If there is evidence of reactivation, a liver specialist should be consulted.

Malignancy (including non-melanoma skin cancer)

Malignancies, including non-melanoma skin cancer (NMSC) have been reported in patients receiving ritlecitinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis (RA) patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and NMSC, was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors.

In patients 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g., current malignancy or history of malignancy), ritlecitinib should only be used if no suitable treatment alternatives are available.

Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Major adverse cardiovascular events (MACE)

Events of MACE have been reported in patients receiving ritlecitinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke was observed with tofacitinib compared to TNF inhibitors.

Therefore, in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, ritlecitinib should only be used if no suitable treatment alternatives are available.

Venous thromboembolism (VTE)

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving ritlecitinib.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in RA patients 50 years and older with at least one additional cardiovascular risk factor, a dose-dependent higher rate of VTE including DVT and PE was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) ritlecitinib should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, ritlecitinib should be used with caution. VTE risk factors other than cardiovascular or malignancy risk

factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder.

Patients should be re-evaluated periodically during ritlecitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue ritlecitinib in patients with suspected VTE, regardless of dose.

Neurological events

Ritlecitinib-related axonal dystrophy has been observed in chronic Beagle dog toxicity studies (see section 5.3). Treatment with ritlecitinib should be discontinued in case unexplained neurological symptoms occur.

Haematologic abnormalities

Treatment with ritlecitinib was associated with decreases in lymphocytes and platelets (see section 4.8). Prior to initiating treatment with ritlecitinib, ALC and platelet counts should be performed. Treatment with ritlecitinib should not be initiated in patients with an ALC $< 0.5 \times 10^3/mm^3$ or a platelet count $< 100 \times 10^3/mm^3$. After initiating treatment with ritlecitinib, treatment interruption or discontinuation are recommended based on ALC and platelet count abnormalities (see section 4.2). ALC and platelet counts are recommended at 4 weeks after initiation of therapy with ritlecitinib, and thereafter according to routine patient management.

Vaccinations

No data are available on the response to vaccination in patients receiving ritlecitinib. Use of live attenuated vaccines should be avoided during or immediately prior to ritlecitinib treatment. Prior to initiating ritlecitinib, it is recommended that patients are brought up to date with all immunisations, including prophylactic herpes zoster vaccinations, in agreement with current immunisation guidelines.

Use in patients 65 years of age and older

There are limited data in patients ≥ 65 years of age. Age appeared to be a risk factor for lower ALC in patients ≥ 65 years of age.

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large randomised study of tofacitinib (another JAK inhibitor), ritlecitinib should only be used in these patients if no suitable treatment alternatives are available.

Excipients with known effect

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of ritlecitinib

The coadministration of multiple 200 mg doses of itraconazole, a strong CYP3A inhibitor, increased the area under curve $(AUC)_{inf}$ of ritlecitinib by approximately 15%. This is not considered clinically significant and, therefore dose adjustment is not required when ritlecitinib is coadministered with CYP3A inhibitors.

The coadministration of multiple 600 mg doses of rifampicin, a strong inducer of CYP enzymes, decreased the AUC_{inf} of ritlecitinib by approximately 44%. This is not considered clinically significant and, therefore dose adjustment is not required when ritlecitinib is coadministered with inducers of CYP enzymes.

Potential for ritlecitinib to affect the pharmacokinetics of other medicinal products

Multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of midazolam a CYP3A4 substrate, by approximately 2.7-fold and 1.8-fold, respectively. Ritlecitinib is a moderate inhibitor of CYP3A; caution should be exercised with concomitant use of ritlecitinib with CYP3A substrates (e.g., quinidine, cyclosporine, dihydroergotamine, ergotamine, pimozide) where moderate concentration changes may lead to serious adverse reactions. Dose adjustment recommendations for the CYP3A substrate (e.g., colchicine, everolimus, tacrolimus, sirolimus) should be considered.

Multiple doses of 200 mg once daily ritlecitinib increased the AUC_{inf} and C_{max} of caffeine, a CYP1A2 substrate, by approximately 2.7-fold and 1.1-fold, respectively. Ritlecitinib is a moderate inhibitor of CYP1A2; caution should be exercised with concomitant use of ritlecitinib with other CYP1A2 substrates (e.g., tizanidine) where moderate concentration changes may lead to serious adverse reactions. Dose adjustment recommendations for the CYP1A2 substrate (e.g., theophylline, pirfenidone) should be considered.

The coadministration of a single 400 mg dose of ritlecitinib increased the AUC_{inf} of sumatriptan (an organic cation transporter [OCT]1 substrate) by approximately 1.3 to 1.5-fold relative to sumatriptan dose given alone. The increase in sumatriptan exposure is not considered clinically relevant. Caution should be exercised with concomitant use of ritlecitinib with OCT1 substrates where small concentration changes may lead to serious adverse reactions.

Ritlecitinib did not produce clinically significant changes in the exposures of oral contraceptives (e.g., ethinyl oestradiol or levonorgestrel), CYP2B6 substrates (e.g., efavirenz), CYP2C substrates (e.g., tolbutamide), or substrates of organic anion transporter (OAT)P1B1, breast cancer resistant protein (BCRP), and OAT3 (e.g., rosuvastatin).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Ritlecitinib is not recommended in women of childbearing potential not using contraception. Women of childbearing potential have to use effective contraception during treatment and for 1 month following the final dose of Litfulo.

Pregnancy

There are no or limited data from the use of ritlecitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Ritlecitinib was teratogenic in rats and rabbits at high doses (see section 5.3). Litfulo is contraindicated during pregnancy (see section 4.3).

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of ritlecitinib in milk (see section 5.3). A risk to newborns/infants cannot be excluded. Litfulo is contraindicated during breast-feeding (see section 4.3).

Fertility

The effect of ritlecitinib on human fertility has not been evaluated. There were no effects on fertility in rats at clinically relevant exposures (see section 5.3).

4.7 Effects on ability to drive and use machines

Litfulo 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 are diarrhoea (9.2%), acne (6.2%), upper respiratory tract infections (6.2%), urticaria (4.6%), rash (3.8%), folliculitis (3.1%), and dizziness (2.3%).

Tabulated list of adverse reactions

A total of 1630 patients were treated with ritlecitinib representing 3751 patient-years of exposure. Three placebo-controlled studies were integrated (130 participants on 50 mg daily and 213 participants on placebo) to evaluate the safety of ritlecitinib in comparison to placebo for up to 24 weeks after treatment initiation.

Table 2 lists all adverse reactions observed in alopecia areata placebo-controlled studies presented by system organ class and frequency, using the following categories: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions

System organ class	Common	Uncommon
Infections and infestations	Herpes zoster Folliculitis Upper respiratory tract infections	
Nervous system disorders	Dizziness	
Gastrointestinal disorders	Diarrhoea	
Skin and subcutaneous tissue disorders	Acne Urticaria Rash	
Investigations	Blood creatine phosphokinase increased	Platelet count decreased Lymphocyte count decreased Alanine aminotransferase increased > 3 × ULN[a] Aspartate aminotransferase increased > 3 × ULN[a]

a. Includes changes detected during laboratory monitoring

Description of selected adverse reactions

Infections
In the placebo-controlled studies, for up to 24 weeks, overall infections have been reported in 31% of patients (80.35 per 100 patient-years) treated with placebo and 33% of patients (74.53 per 100 patient-years) treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, overall infections were reported in 51% of patients (89.32 per 100 patient-years) treated with ritlecitinib 50 mg or higher.

Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, overall infections were reported in 56.3% of patients (45.3 per 100 patient-years) treated with ritlecitinib 50 mg or higher. Most infections were mild or moderate in severity.

In the placebo-controlled studies the percentage of patients reporting infection-related adverse reaction of herpes zoster were 1.5% in the ritlecitinib 50 mg group compared to 0 in placebo. All herpes zoster events were non-serious; 1 patient receiving ritlecitinib 200/50 mg (200 mg once daily for 4 weeks followed by 50 mg once daily) experienced an event of varicella zoster virus infection that met criteria as an opportunistic infection (multi-dermatomal herpes zoster). In study AA-I, for up to 48 weeks, 2.3% of patients (2.61 per 100 patient-years) treated with ritlecitinib 50 mg or higher reported herpes zoster Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, the rate of herpes zoster was 1.05 per 100 patient-years in patients treated with ritlecitinib 50 mg or higher.

In the placebo-controlled studies, for up to 24 weeks, no serious infections were reported in patients treated with placebo or ritlecitinib 50 mg. The proportion and rate of serious infections in patients treated with ritlecitinib 200/50 mg was 0.9% (2.66 per 100 patient-years). In study AA-I, for up to 48 weeks, serious infections were reported in 0.8% of patients (0.86 per 100 patient-years) treated with ritlecitinib 50 mg or higher. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, the proportion and rate of serious infection in ritlecitinib 50 mg or higher was 1.3% (0.57 per 100 patient-years).

Opportunistic infections
Opportunistic infections of multi-dermatomal herpes zoster were reported in 1 patient (0.50 per 100 patient-years) treated with ritlecitinib 200/50 mg in the placebo-controlled studies, no patients in study AA-I, for up to 48 weeks, and 4 patients (0.12 per 100 patient-years) treated with ritlecitinib 50 mg or higher in the integrated safety analysis, including the long-term study and a study in vitiligo. Cases of opportunistic herpes zoster were mild or moderate in severity.

Decreased lymphocyte count
In the placebo-controlled studies, for up to 24 weeks, and study AA-I, for up to 48 weeks, treatment with ritlecitinib was associated with a decrease in lymphocyte count. Maximum effects on lymphocytes were observed within 4 weeks, after which lymphocyte count remained stable at a lower level with continued therapy. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, confirmed ALC $< 0.5 \times 10^3/mm^3$ occurred in 3 participants (0.2%) treated with ritlecitinib 50 mg.

Decreased platelet count
In the placebo-controlled studies, for up to 24 weeks, and study AA-I, for up to 48 weeks, treatment with ritlecitinib was associated with a decrease in platelet count. Maximum effects on platelets were observed within 4 weeks, after which platelet count remained stable at a lower level with continued therapy. Among all patients treated with ritlecitinib in the integrated safety analysis, including the long-term study and a study in vitiligo, 2 patients (0.1%) treated with ritlecitinib 50 mg or higher had a confirmed platelet count $< 100 \times 10^3/mm^3$.

Creatine phosphokinase (CPK) elevations
In the placebo-controlled studies, for up to 24 weeks, events of blood CPK increased were reported in 2 patients (1.5%) treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, events of blood CPK increased were reported in 3.8% of patients treated with ritlecitinib 50 mg or higher. CPK elevations >5x upper limit of normal (ULN) were reported in 2 (0.9%) of patients treated with placebo and 5 (3.9%) of patients treated with ritlecitinib 50 mg. In study AA-I, for up to 48 weeks, CPK

elevations >5x ULN were reported in 6.6% of patients treated with ritlecitinib 50 mg or higher. Most elevations were transient and none led to discontinuation.

Increased transaminases
In the placebo-controlled studies, for up to 24 weeks, events of increases in ALT and AST values (>3 × ULN) were reported in 3 patients (0.9%) and 2 patients (0.6%) treated with ritlecitinib 50 mg or higher, respectively. Most elevations were transient, and none led to discontinuation.

Paediatric population

A total of 181 adolescents (12 to < 18 years of age) were enrolled in ritlecitinib alopecia areata studies.

The safety profile observed in adolescents was similar to that of the adult population.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Ritlecitinib was administered in placebo-controlled studies up to a single oral dose of 800 mg and multiple oral doses of 400 mg daily for 14 days. No specific toxicities were identified. In case of overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions (see section 4.8). There is no specific antidote for overdose with ritlecitinib. Treatment should be symptomatic and supportive.

Pharmacokinetics (PK) data up to and including a single oral dose of 800 mg in healthy adult volunteers indicate that more than 90% of the administered dose is expected to be eliminated within 48 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Janus-associated kinase (JAK) inhibitors, ATC code: L04AF08

Mechanism of action

Ritlecitinib irreversibly and selectively inhibits Janus kinase (JAK) 3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family by blocking the adenosine triphosphate (ATP) binding site. In cellular settings, ritlecitinib specifically inhibits γ-common cytokines (IL-2, IL-4, IL-7, IL-15 and IL-21) signalling through JAK3-dependent common-γ chain receptors. Additionally, ritlecitinib inhibits TEC family of kinases, resulting in reduced cytolytic activity of NK cells and CD8+ T cells.

JAK3 and TEC family mediated signalling pathways are both involved in alopecia areata pathogenesis, although complete pathophysiology is still not understood.

Pharmacodynamic effects

Lymphocyte subsets
In patients with alopecia areata, treatment with ritlecitinib was associated with dose-dependent early decreases in absolute lymphocyte levels, T lymphocytes (CD3) and T lymphocyte subsets (CD4 and

CD8). After the initial decrease, the levels partially recovered and remained stable up to 48 weeks. There was no change observed in B lymphocytes (CD19) in any treatment group. There was a dose-dependent early decrease in NK cells (CD16/56) which remained stable at the lower level up to Week 48.

Immunoglobulins
In patients with alopecia areata, treatment with ritlecitinib was not associated with clinically meaningful changes in Immunoglobulin (Ig)G, IgM or IgA up to Week 48, indicating a lack of systemic humoral immunosuppression.

Clinical efficacy and safety

The efficacy and safety of ritlecitinib was evaluated in a pivotal, randomised, double-blind, placebo-controlled study (study AA-I) in alopecia areata patients 12 years of age and older with ≥ 50% scalp hair loss, including alopecia totalis and alopecia universalis. The dose-response of ritlecitinib was also evaluated in this study. The study treatment period consisted of a placebo-controlled 24-week period and a 24-week extension period. Study AA-I evaluated a total of 718 patients who were randomised to one of the following treatment regimens for 48 weeks: 1) 200 mg once daily for 4 weeks followed by 50 mg once daily for 44 weeks; 2) 200 mg once daily for 4 weeks followed by 30 mg once daily for 44 weeks; 3) 50 mg once daily for 48 weeks; 4) 30 mg once daily for 48 weeks; 5) 10 mg once daily for 48 weeks; 6) placebo for 24 weeks followed by 200 mg once daily for 4 weeks and 50 mg once daily for 20 weeks; or 7) placebo for 24 weeks followed by 50 mg for 24 weeks.

This study assessed as primary outcome the proportion of subjects who achieved a SALT (Severity of Alopecia Tool) score of ≤ 10 (90% or more scalp hair coverage) at Week 24. Additionally, this study assessed as key secondary outcome the Patient's Global Impression of Change (PGI-C) response at Week 24 and also assessed as secondary outcomes SALT score of ≤ 20 (80% or more scalp hair coverage) at Week 24 and improvements in regrowth of eyebrows and/or eyelashes at Week 24.

Baseline characteristics
Male or female patients 12 years of age and older, were assessed in study AA-I. All patients had alopecia areata with ≥ 50% scalp hair loss (SALT [Severity of Alopecia Tool] score ≥ 50) without evidence of terminal hair regrowth within the previous 6 months and with the current episode of scalp hair loss ≤ 10 years and no other known cause of hair loss (e.g., androgenetic alopecia).

Across all treatment groups 62.1% were female, 68.0% were White, 25.9% were Asian, and 3.8% were Black or African American. The mean age of patients was 33.7 years and the majority (85.4%) were adults (≥ 18 years of age). A total of 105 (14.6%) patients 12 to < 18 years of age and 20 (2.8%) patients 65 years of age and older were enrolled. The mean (SD) baseline absolute SALT score ranged from 88.3 (16.87) to 93.0 (11.50) across treatment groups; among patients without alopecia totalis/alopecia universalis at baseline, the mean SALT score ranged from 78.3 to 87.0. The majority of patients had abnormal eyebrows (83.0%) and eyelashes (74.7%) at baseline across treatment groups. The median duration since alopecia areata diagnosis was 6.9 years and the median duration of the current alopecia areata episode was 2.5 years. Randomisation was stratified by alopecia totalis/alopecia universalis status with 46% of patients classified as alopecia totalis/alopecia universalis based upon a baseline SALT score of 100.

Clinical response
A significantly greater proportion of patients achieved SALT ≤ 10 response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 3). The SALT ≤ 10 response rate for ritlecitinib 50 mg increased further at Week 48 (Figure 1).

A significantly greater proportion of patients achieved Patient's Global Impression of Change (PGI-C) response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 3) with response rates continuing to increase through Week 48 (Figure 1).

A significantly greater proportion of patients achieved a SALT ≤ 20 response with ritlecitinib 50 mg compared to placebo at Week 24 (Table 3). The SALT ≤ 20 response rate increased further at Week 48.

Improvements in regrowth of eyebrows and/or eyelashes were seen at Week 24 (Table 3) with ritlecitinib 50 mg among patients with abnormal eyebrows and/or eyelashes at baseline with further increases seen at Week 48.

Treatment effects at Week 24 in subgroups (age, gender, race, region, weight, duration of disease since diagnosis, duration of current episode, prior pharmacologic treatment) were consistent with the results in the overall study population. Treatment effects at Week 24 in the alopecia totalis/alopecia universalis subgroup were lower compared to the non-alopecia totalis/non-alopecia universalis subgroup. Treatment effects at Week 24 in adolescents 12 to less than 18 years of age were consistent with the results in the overall study population.

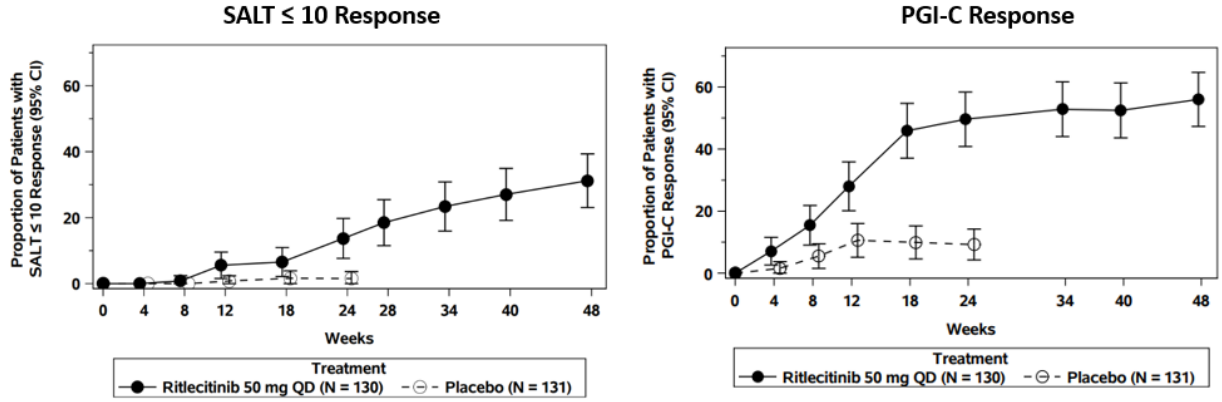
Table 3. Efficacy results of ritlecitinib at week 24

Endpoint	Ritlecitinib 50 mg once daily (N = 130) % Responders	Placebo (N = 131) % Responders	Difference from placebo (95% CI)
SALT ≤ 10 response[a,b]	13.4	1.5	11.9 (5.4, 18.3)
PGI-C response[b,c]	49.2	9.2	40.0 (28.9, 51.1)
SALT ≤ 20 response[d,e]	23.0	1.6	21.4 (13.4, 29.5)
EBA response[f]	29.0	4.7	24.3 (14.8, 34.5)
ELA response[g]	28.9	5.2	23.7 (13.6, 34.5)

Abbreviations: EBA = eyebrow assessment; ELA = eyelash assessment; CI = confidence interval; N = total number of patients; PGI-C = Patient's Global Impression of Change; SALT = Severity of Alopecia Tool

a. SALT ≤ 10 responders were patients with scalp hair loss of ≤ 10%. SALT scores range from 0 to 100 with 0 = no scalp hair loss and 100 = total scalp hair loss.
b. Statistically significant with adjustment for multiplicity.
c. PGI-C responders were patients with a score of "moderately improved" or "greatly improved" based upon a 7-point scale from "greatly improved" to "greatly worsened".
d. SALT ≤ 20 responders were patients with scalp hair loss of ≤ 20%. SALT scores range from 0 to 100 with 0 = no scalp hair loss and 100 = total scalp hair loss.
e. Statistically significant.
f. EBA response is defined as at least a 2-grade improvement from baseline or normal EBA score on a 4-point scale in patients with abnormal eyebrows at baseline.
g. ELA response is defined as at least a 2-grade improvement from baseline or normal ELA score on a 4-point scale in patients with abnormal eyelashes at baseline.

Figure 1. SALT ≤ 10 and PGI-C response through Week 48



Abbreviations: CI = confidence interval; N = total number of patients; PGI-C = Patient Global Impression of Change; QD = once daily; SALT = Severity of Alopecia Tool

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ritlecitinib in one or more subsets of the paediatric population in the treatment of alopecia areata (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute oral bioavailability of ritlecitinib is about 64%. Based on oral and intravenous administration of the labelled active substance, the relative urinary recovery (oral/intravenous) of labelled compounds was about 89%, indicating a high fraction absorbed (f_a). Peak plasma concentrations are reached within 1 hour following multiple oral doses. Food does not have a clinically significant impact on the extent of ritlecitinib absorption, as a high-fat meal decreased the ritlecitinib C_{max} by ~ 32% and increased AUC_{inf} by ~11%. In placebo-controlled studies, ritlecitinib was administered without regard to meals (see section 4.2).

In vitro, ritlecitinib is a substrate of P-glycoprotein (P-gp) and BCRP. However, as ritlecitinib has a high fraction absorbed (f_a) with both C_{max} and AUC increases in a dose proportional manner (20 – 200 mg single dose range), P-gp and BCRP are not expected to have a meaningful impact on the absorption of ritlecitinib.

Distribution

After intravenous administration, the volume of distribution of ritlecitinib is about 74 L. Approximately 14% of circulating ritlecitinib is bound to plasma proteins, primarily albumin. The blood/plasma distribution ratio of ritlecitinib is 1.62. Ritlecitinib is a covalent inhibitor that has been shown to bind to off-target proteins such as MAP2K7, DOCK10, albumin, CYP1A2, CYP3A, UGT1A1, and UGT1A4, some of which may have clinical relevance in drug interactions (see section 4.5).

Biotransformation

The metabolism of ritlecitinib is mediated by multiple isoforms of Glutathione S-transferase (GST: cytosolic GST A1/3, M1/3/5, P1, S1, T2, Z1, and microsomal Membrane Associated Proteins involved in Eicosanoid and Glutathione metabolism [MAPEG]1/2/3) and CYP enzymes (CYP3A, CYP2C8, CYP1A2, and CYP2C9), with no single clearance route contributing more than 25%. Hence, medicinal products inhibiting a selective metabolic pathway are unlikely to impact the systemic

exposures of ritlecitinib. Specific inhibitors of transporters are unlikely to result in clinically relevant changes in the bioavailability of ritlecitinib.

In a human radiolabeled study, ritlecitinib was the most prevalent circulating species (30.4% of circulating radioactivity) after oral administration, with a major cysteine conjugate metabolite M2 (16.5%), which is pharmacologically inactive.

Elimination

Ritlecitinib is eliminated primarily by metabolic clearance mechanisms, with approximately 4% of the dose excreted as unchanged active substance in urine. Approximately 66% of radiolabeled ritlecitinib dose is excreted in the urine and 20% in the faeces. Following multiple oral doses, steady state was reached approximately by Day 4 due to non-stationary PK. The steady state PK parameters of AUC_{tau} and C_{max} appeared to increase in an approximately dose-proportional manner up to 200 mg with the mean terminal half-life ranging from 1.3 to 2.3 hours.

Special populations

Body weight, gender, genotype, race and age
Body weight, gender, GST P1, M1, and T1 genotype, race and age did not have a clinically meaningful effect on ritlecitinib exposure.

Adolescents (≥ 12 to < 18 years)
Based on population PK analysis, there was no clinically relevant difference in ritlecitinib exposures in adolescent patients compared to adults.

Paediatric (< 12 years)
The PK of ritlecitinib in children under 12 years of age have not yet been established.

Renal impairment

The AUC_{24} and C_{max} in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min) was about 55% and 44% higher, respectively, compared with matched participants with normal renal functions. This was confirmed by popPK analysis. These differences are not considered clinically significant. Ritlecitinib was not studied in patients with mild (eGFR 60 to < 90 mL/min) or moderate (eGFR 30 to < 60 mL/min) renal impairment. However, based on the results obtained in patients with severe renal impairment, a clinically significant increase in ritlecitinib exposure is not expected in these patients. The eGFR and classification of renal function status of participants was done using the Modification of Diet in Renal Disease (MDRD) formula.

Based on the above considerations, no dose adjustment is required in patients with mild, moderate or severe renal impairment. Ritlecitinib has not been studied in patients with ESRD or in renal transplant recipients (see section 4.2).

Hepatic impairment

Patients with moderate (Child Pugh B) hepatic impairment had an 18.5% increase in ritlecitinib AUC_{24} compared to participants with normal hepatic function. Ritlecitinib was not studied in patients with mild (Child Pugh A) hepatic impairment. However, based on the results obtained in patients with moderate hepatic impairment, a clinically significant increase in ritlecitinib exposure is not expected in these patients. No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 4.2). Ritlecitinib has not been studied in patients with severe (Child Pugh C) hepatic impairment (see section 4.3).

5.3 Preclinical safety data

General toxicity

Decreased lymphocyte counts and decreased lymphoid cellularity of organs and tissues of the immune and haematolymphopoietic systems were observed in nonclinical toxicity studies and were attributed to the pharmacological properties (JAK3/TEC inhibition) of ritlecitinib.

Chronic administration of ritlecitinib to Beagle dogs led to the occurrence of axonal dystrophy at systemic exposures of at least 7.4-times the expected exposure in patients treated with 50 mg per day (based on unbound AUC24). Axonal dystrophy is presumably related to binding to off-target neuronal proteins. It is not known if axonal dystrophy occurred in dogs at lower systemic exposures. At a systemic exposure that was 33-times above the expected exposure in patients treated with 50 mg per day (based on unbound AUC24), axonal dystrophy was associated with neurological hearing loss. While these findings proved to reverse after dosing cessation of ritlecitinib in dogs, a risk to patients at a chronic dosing regimen cannot be fully excluded (see section 4.4).

Genotoxicity

Ritlecitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). Ritlecitinib is not aneugenic or clastogenic at exposures equal to 130 times the MRHD on an unbound AUC basis based on the results of the *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

No evidence of tumorigenicity was observed in the 6-month Tg.ras H2 mice administered ritlecitinib at exposures equal to 11 times the MRHD on an unbound AUC basis. In a 2-year rat carcinogenicity study, a higher incidence of benign thymomas in female rats and benign thyroid follicular adenomas in male rats was noted following ritlecitinib administration at exposures equal to 29 times the MRHD on an unbound AUC basis. At this ritlecitinib exposure, a higher incidence of malignant thymomas in female rats cannot be excluded. No ritlecitinib-related thymomas or thyroid follicular adenomas were observed at exposures equal to 6.3 times the MRHD on an unbound AUC basis.

Reproductive and developmental toxicity

Ritlecitinib had no effects on female rat fertility at exposures equal to 55 times the MRHD on an unbound AUC basis. Effects on male rat fertility were noted (higher preimplantation loss resulting in lower number of implantation sites and corresponding lower litter size in naïve females mated with ritlecitinib dosed males) at exposure equal to 55 times the MRHD on an unbound AUC basis. No effects on male fertility were noted at exposures equal to 14 times the MRHD on an unbound AUC basis. No effects on spermatogenesis (sperm counts, sperm production rate, motility, and morphology) were noted at any dose in the rat fertility study.

In an embryo-foetal development study in pregnant rats, oral administration of ritlecitinib from gestation days 6 to 17 resulted in foetal skeletal malformations and variations and lower foetal body weights at exposures greater than or equal to 49 times the unbound AUC at the MRHD (see section 4.3). There were no effects on embryo-foetal development at exposures equal to 16 times the unbound AUC at the MRHD.

In an embryo-foetal development study in pregnant rabbits, oral administration of ritlecitinib from gestation days 7 to 19 resulted in lower mean foetal body weights and higher incidences of visceral malformations, skeletal malformations, and skeletal variations at exposures equal to 55 times the unbound AUC at the MRHD (see section 4.3). There were no effects on embryo-foetal development at exposures equal to 12 times the unbound AUC at the MRHD.

In a rat pre- and postnatal development study, oral administration of ritlecitinib from gestation day 6 through lactation day 20 resulted in developmental toxicity that included lower postnatal survival,

lower offspring body weights, and secondary developmental delays at exposure equal to 41 times the unbound AUC at the MRHD (see section 4.3). Bred females in the F1 generation exhibited lower mean numbers of corpora lutea at exposures equal to 41 times the unbound AUC at the MRHD. There were no effects on pre- and postnatal development at exposures equal to 14 times the unbound AUC at the MRHD.

In a juvenile rat toxicity study, oral administration of ritlecitinib from postnatal day 10 to 60 (comparable to infant through adolescence human age) was not associated with effects on the nervous or skeletal systems.

Lactation

Following administration of ritlecitinib to lactating rats, concentrations of ritlecitinib in milk over time were higher than those in plasma, where the mean milk to plasma AUC ratio was determined to be 2.2 (see section 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsule content

Cellulose microcrystalline
Lactose monohydrate
Crospovidone
Glycerol dibehenate

Hard capsule shell

Hypromellose (E464)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Brilliant Blue FCF (E133)

Printing ink

Shellac
Propylene glycol
Ammonia solution concentrated
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a silica gel desiccant and polypropylene closure containing 28 hard capsules.

OPA/Al/PVC/Al blisters containing 10 hard capsules. Each pack contains 30 or 90 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1755/001
EU/1/23/1755/002
EU/1/23/1755/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

15/09/2023

10. DATE OF REVISION OF THE TEXT

09/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Ref: LT 3_0