A REVOLUTIONARY DRUG: RITLECITINIB

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Abstract: Patchy hair loss is a symptom of alopecia areata (AA), an autoimmune condition that impacts up to 147 million individuals globally. For widespread and enduring illness, there currently exist few viable treatment choices, since there are no medicines approved by the FDA particularly for AA. Even for those with chronic, severe diseases, a medicine that has a favorable clinical response and a benefit-risk ratio suitable for long-term usage is still required. Numerous investigations and case studies that evaluated Janus kinase inhibitors came up with favorable results. It has been demonstrated that the JAK3/TEC kinase inhibitor ritlecitinib prevents immune cells from producing and signaling molecules that lead to hair loss in alopecia areata patients. Additionally, several kinds of clinical trials are examining the efficacy of ritlecitinib in the treatment of patients with melanoma autoimmune illnesses, including as Crohn's disease and colitis brought on by ulcers. Ritlecitinib's use has the advantage of avoiding the clinical effects of JAK1/JAK2 suppression, such as raised cholesterol and liver enzymes, and those connected to JAK2 restrictions (thrombocytopenia & anemia). This is in contrast to other non-select JAK inhibitors. Psychotherapy with Ritlecitinib 50 mg, 30 mg daily for an average of 24 weeks have been shown to result in hair regrowth, with a substantial number of patients achieving SALT 20 (20% of scalp hair loss) during a six-month period of chemotherapy compared to placebo. More investigation is necessary to determine the long-term effects.

Keywords: CYP enzymes, cytotoxic clusters, Pharmacokinetics, Janus kinase inhibitor, immunosuppressants

I. Discovery and further history

Alopecia rhinitis is an autoimmune condition that causes inflammation and results in patches of hair loss that, in more severe cases, can result in complete body baldness. There are few effective treatments available, and there is no known cure, however medications occasionally cause long-lasting remission. Even people who completely regrow their hair after therapy are susceptible to recurrence, therefore disease control can't be assured. Prior to June 23, no medication was FDA-approved as being the safest to use in youngsters, but patients with alopecia who are 12 and older can now take it. In the United States, 6.7 million people suffer with alopecia.

An autoimmune condition called alopecia areata results in patchy hair loss, primarily on the area around the head but occasionally also on the appearance and other body parts. Although it can afflict older persons' children and teenagers, the average age of onset is between 25 and 35 years. [1,2]

Ritlecitinib is the pioneer drug in a novel class of crosslinking kinase inhibitors that has excellent janus kinase 3 (JAK3) selectivity. Ritlecitinib has been demonstrated in laboratory studies to block the activity of immune cells and signaling molecules that result in chronic hair loss in alopecia patients.

A JAK3 inhibitor that is irreversible, ritlecitinib, was also reported. These inhibitors' chemical structures contain covalent bonds that create groups like acrylamide and alpha cyanoacrylamide that can attach to the Cys909 residue. [3,4,5]

According to Angela Hwang, the director of commercial affairs and president of Pfizer's global biopharmaceuticals business, Litfulo represents an important step forward for alopecia areata, an autoimmune illness for which there was no FDA-approved treatment for teenagers and just a few options accessible for adults.

Adults as well as adolescents who suffer from major hair loss now have the chance to experience significant scalp hair restoration.

Pfizer releases encouraging Top-Line findings from the phase 2b/3 Trail of ritlecitinib in Alopecia Areata on August 4, 2021. Ritlecitib, manufactured by Pfizer, is approved by the FDA and EMA for use in patients with alopecia areata who are 12 years of age or older as of September 9, 2022. FDA grants approval for Litfulo (ritlecitinib) on June 23, 2023 for use in adults as well as teens with severe Alopecia Areata.

II. Physicochemical properties

i] Solubility: A test tube: DMSO: 125 mg/ML (438.07 mM; ultrasonic required) Water: 6.67 mg/ML (23.38 mM); ultrasonic required. In Vivo To each solvent, add 0.5% MC followed by Tween-80; solubility 6.67 mg (23.38 mM)/mL required ultrasonic for suspended solution [6]

ii] Melting point: The melting point of ritlecitinib is 199°C [14]

III. Pharmocokinetics properties

[i] **BCS CLASSIFICATION**: Ritlecitinib comes under type II which is low solubility and high permeability.

Ii] Tmax	iii] Cmax	iv] T-half
Ritlecitinib's AUC0-tau increases up to 200 mg in a roughly dose-proportional manner. AUCinf increased by 11% when a high-fat meal and a 100mg ritlecitinib pill were delivered together.	Ritlecitinib's Cmax rises to 200 mg in a roughly dose-proportional way, A high-fat meal and a 100 mg ritlecitinib pill given together reduced Cmax by 32%.	Ritlecitinib half is calculated by using formula t1/2=0.693*(vd/CL) vd=1.3 L/kg2 CL=5.6 mL/min/kg2

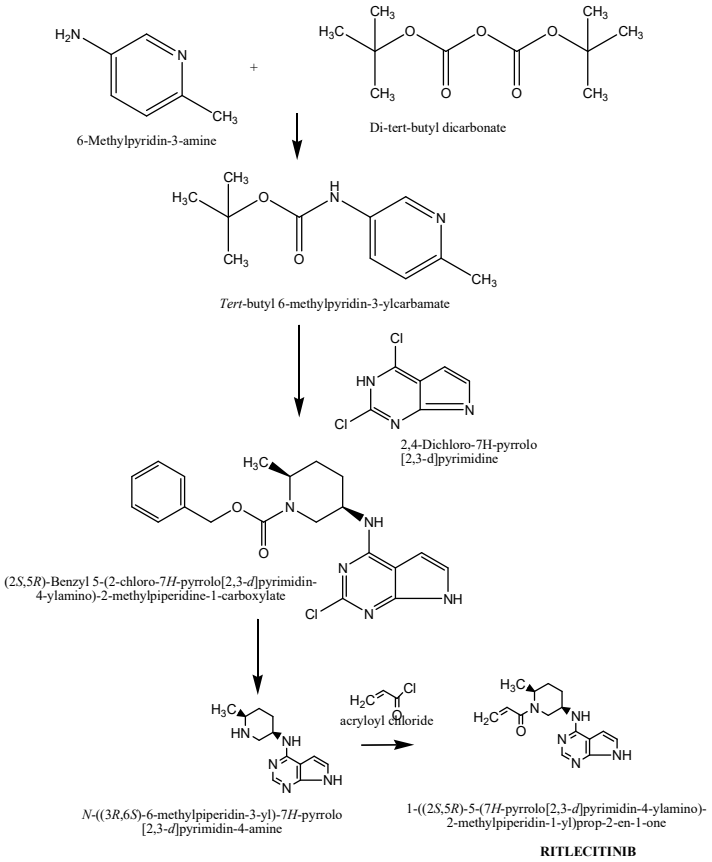
ABSORPTION	DISTRIBUTION	ELIMINATION	METABOLISM	EXCRETION
The total oral bioavailability is roughly 64%. Within one hour, ritlecitinib peak plasma concentrations were attained.	Plasma proteins bind about 14% of the circulating ritlecitinib.	The mean terminal half-life of ritlecitinib ranges from 1.3 hours to 2.3 hours.	Multiple pathways mediate the metabolism, with no one process accounting for over twenty-five per cent of the entire metabolism. The first of these mechanisms is glutathione S-transferase (GST). 2. CYP enzymes, specifically CYP3A, CYP28, CYP1A2, and CYP2C9.	20% of the radiolabeled dosage is eliminated in the feces and 66% are eliminated in the urine. 4% of the dosage is eliminated unaltered in the urine.

IV. Mechanism of action

Litfulo is a kinase inhibitor: An autoimmune condition called alopecia areata results in hair loss, primarily on the hair follicles yet additionally on the skin of the face and various places. Follicles that produce hair are immune-privileged areas that frequently have been defined by the presence of naturally subdued natural killer cells. Disruptions to this mechanism, however, can result in alopecia areata and the loss of immunological privilege. Genome-wide association studies have connected the pathophysiology of alopecia areata to the amplification of UL16-binding protein 3 (ULBP3), a protein which binds to naturally occurring killer cell receptors. The attack of deadly clusters of differentiating 8-positive NK group 2D-positive is encouraged by the overexpression of ULBP3.

Hair follicle dystrophy is caused by T-cells attacking hair follicles. Through the interferon alpha and interleukin 15 signaling pathways, CD8+ (NKG2D+) T Cells encourage the allergic reaction of hair follicles, which then activates the Janus Kinase (JAK)/signal transduction and promoter of transcription (STAT) biochemical pathways. JAK inhibitors have so been suggested as a possible treatment for alopecia areata. [7,8]. By inhibiting the adenosine triphosphate (ATP) binding site, ritlecitinib inhibits Janus Kinase 3 (JAK3) and the tyrosine kinase family expressed in hepatocellular carcinoma (TEC) kinase irreversibly. Ritlecitinib prevents cytokine-induced STAT phosphorylation that is carried out by JAK3-dependent receptors in cellular contexts. Ritlecitinib also prevents immunological receptors that depend on members of the TEC kinase family from signaling. Currently, it is unknown if inhibiting a particular JAK or TEC family enzyme may affect the efficacy of therapy [6].

V. Synthesis



VI. Detailed description

6-methylpyridin3-amine react with Di-tert-butyl-dicarbonate to form tert-butyl6-methylpyridin3-yl carbonate in presence of 2,4 Dichloro-7*H*-pyyrolo[2,3-d] pyrimidine it forms (2S, 5R)-benzyl 5-(2-choloro-7*H*-pyrrolo[2,3-d] pyrimidin-4-ylamino)-2-methylpiperidine-1-carboxylate form ritlecitinib.

Adverse effect

- Herpes zoster
- Appendicitis
- Sepsis
- Thromboembolic events
- Urticaria
- Creatine Phosphokinase Elevations
- Liver Enzyme Elevations [1,9,10]

VII. Treatment of overdose

In clinical trials, up to 800 mg of LITFULO was given orally in one dose. No specific adverse reactions were found, but they were equivalent to those encountered at lower doses. In healthy adult volunteers, pharmacokinetic data up towards and including an individual oral administration of 800 mg show that over ninety per cent of the dose that was given is anticipated to be eliminated within 48 hours.
A specific LITFULO overdose remedy is not available. The patient should be monitored for signs and symptoms of an adverse response while receiving symptomatic and supportive treatment.[11]

Patients need to inform to physician as soon as possible if you are suffering from an infection, receive medical care for one, or exhibit symptoms of one, such as:

- Fever, sweating, or chills
- Muscle aches
- Cough or shortness of breath
- Blood in your phlegm
- Weight loss
- Warm, red, or painful skin or sores on your body
- Diarrhea or stomach pain
- Burning when you urinate or urinating more often than usual
- Feeling very tired

LITFULO might increase your risk of contracting an infection or exacerbate an existing one. Your doctor may stop treating you with LITFULO if you get a serious illness until the infection is under control. People 50 years of age and older who are using a Janus kinase (JAK) inhibitor and have at least one cardiovascular risk factor are at an increased risk of dying. A kinase inhibitor is LITFULO.

Cancer and immune system problems
By altering the way your body's immune system functions, LITFULO could boost your risk of developing certain cancers. Skin malignancies and other cancers, such as lymphoma, are possible. By taking a JAK inhibitor, people, particularly current or former smokers, have an increased chance of developing certain cancers, such as lymphoma and lung cancer. During therapy, check your skin for skin cancer as directed by your healthcare professional. If you or a loved one have ever had cancer of any kind, let your doctor know.
People 50 years of age and older who are susceptible to at least one cardiovascular risk factor and utilize a JAK inhibitor are at a greater risk of suffering a serious cardiovascular event, such as a coronary artery disease, stroke, or death, particularly if they now smoke or have smoked in the past.

Get emergency help right away if you have any symptoms of a heart attack or stroke while taking LITFULO, including:
• Chest discomfort that continues for for in excess of a few minutes or that disappears then reappears
• Extreme chest, throat, neck, or tongue tenseness, pain, pressure, or stiffness
• Chest discomfort or shortness of breath, either alone or in combination with pain in the legs, back, neck, teeth, or stomach
• Sweating profusely; feeling queasy or sick; feeling dizzy; having weakness in one side or area of your body; slurred speech

Blood clots: Some persons taking LITFULO may develop blood clots in their veins in the legs (deep vein blood clots DVT), airways (pulmonary embolism, which PE), or eyes. This could endanger your life. People 50 years

of age and older who are taking a JAK inhibitor and have at least one cardiovascular (cardiovascular) risk factor have a higher incidence of blood clots in the blood vessels of the legs and lungs. If you have ever experienced blood clots, let your doctor know.

If you experience any blood clot signs and symptoms, such as discomfort, swelling, or softness in one or both legs, sudden, unexplained chest pain, upper back pain, shortness of breath, or trouble breathing, or changes in vision, particularly in one eye only, stop taking LITFULO and seek medical attention right away.

Allergic reactions: During LITFULO therapy, it has been reported that some patients experience symptoms that could indicate an allergic reaction. These responses ranged from mild to severe. If you have any allergic reaction symptoms, including as hives, rash, difficulty breathing, feeling weak or dizzy, or thickening of your mouth, tongue, or throat, evacuate LITFULO and get immediate medical attention right once.

Changes in certain laboratory test results: Before you begin taking LITFULO and throughout therapy, your doctor should order blood tests to assess the liver's enzyme and creatine-phosphate kinase (CPK) levels as well as your leukocyte and platelet counts. If your lymphocyte or platelet count are too low or the liver testing are too high, you shouldn't use LITFULO. Blood levels of CPK are frequently elevated in LITFULO patients and can reach dangerous levels. If the findings of these blood tests change, the physician may temporarily halt treatment.

Serious infections. LITFULO might reduce your immune system's capacity to ward off infections. If you have an infection of any kind, wait to start LITFULO until your doctor gives the all-clear. By taking LITFULO or other comparable medications, some patients have experienced significant infections, including tuberculosis (TB) and illnesses brought on by bacteria, fungus, or viruses that may spread throughout the body and require hospitalization. Some individuals on LITFULO-like medications have passed away from these infections. You can have a greater chance of getting shingles (herpes zoster). Before beginning LITFULO medication, your doctor should do a TB test on you. They should also keep a close eye out for any TB symptoms while you are taking LITFULO.

VIII. Indication

A kinase inhibitor called LITFULO is used for adults as well as adolescents 12 years of age and older who have severe alopecia areata.

Limitations of Use: Combining additional JAK inhibitors, biologic immunomodulators, cyclosporine, or other strong immunosuppressants is not advised.

Contraindication

Patients taking LITFULO in clinical trials have experienced severe reactions, including anaphylactic reaction, urticaria, and rash. LITFULO is contraindicated to individuals with a history of hypersensitivity to ritlecitinib or anyone of its excipients. In the event of a clinically serious hypersensitive reaction, stop taking LITFULO and start the necessary treatment.

- Headache
- Diarrhea
- Acne
- Rash
- Urticaria
- Folloculitis
- Pyerxia
- Dermatitis atopic
- Dizziness

IX. Interaction

1) Abatacept - When coupled with ritlecitinib, the risk or severity of side effects may increase.
2) Abemaciclib - When coupled with ritlecitinib, abemaciclib's serum levels can be raised.
3) Abiraterone - When coupled with ritlecitinib, abiraterone's serum levels can be raised.
4) Acyclovir: When coupled with ritlecitinib, acyclovir's serum levels can be raised.
5) Ritlecitinib's AUC and Cmax may be decreased by rifampicin, which could lead to clinical response loss or reduction.
6) Rifampin-by decreasing the hepatic/intestinal enzyme CYP3A4 metabolism-will lower the level or action of ritlecitinib. [11,12]

X. Conventional Marketed Formulation

TYPES	BRAND NAME	COMPANY NAME	DOSE	PRIZE
Capsule	LITFULO	Pfizer	5mg 10mg 25mg 50mg	6,5636 10,255.25 20,510.50 31,996.38

XI. Patent

LITFULO (Ritlecitinib) capsule inventor: Lauren E. Ingram; Reference ID:5196496; Starting process approved-NDA 215830; Approved by: Federal Food Drug and Cosmetic Act (FDCA)
International patent classification: C07D 471/04 (2006.01); A61K 31/4375 (2006.01); C07D 487/04 (2006.01); A61P 35/00 (2006.01); International Application Number: PCT/IB2014/066202; International Filling Date: 20 November 2014; Filling and Publication Language: English; Applicant: Pfizer INC [US/US]; 235 East 42nd Street, New York 10017(US); **Inventors:** BROWN, Mathew Frank, Massachusetts, CHE, Ye, COE-Jotham Wadsworth, FLANGAN, Mark Edward, GILBERT, Adam Matthew, HAYWARD, Matthew Merrill, LANGILLE, Jonathan David, MONTGOMERY, Justin Ian, TELLIEZ, Jean-Baptiste, THORARENSEN, Atli, UNWALLA, Rayomand Jal,

XII. Conclusion

Ritlecitinib rise in the SALT scores was positively connected with the expression of TH1 markers, however the total number of hair keratin proteins was inversely related. Larger and lengthier clinical studies are required. It was effective, well-tolerated, and might be an alternative for alopecia areata sufferers who are old enough to receive systemic therapy.

XIII. References

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