CT Application(s) Summary Report

- **Protocol title:** A Phase 3 Multicenter, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lutikizumab in Adult and Adolescent Subjects with Moderate to Severe Hidradenitis Suppurativa
- **Protocol code number: M20-465**
- ***Public Registry Number:*** EU-CT:2024-510730-40-00
- **Version:** 1.0
- **Date:** 1 March 2024

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Sponsor: Abbvie**
- **Indication:** Hidradenitis Suppurativa
- **Investigator's brochure (IB)**

Version: 9.0
Date: 30\04\2024

- **Name of all Sites:**

1.Air Force Specialized Hospital.
2. Alexanderia University Hospital (2 sites).
3.Ain Shams University Hospital.

- **Name of PI(s):**

1.Air Force Specialized Hospital (PI: Rehab Hegazy)
2.Alexanderia University Hospital Site 1(PI: Tarek Hussein) and site 2(PI: Naglaa Fathy)
3.Ain Shams University Hospital **(**PI: Mahmoud Abdallah)

- **EDA approval date:** 04 October 2025

- **Summary of pre-clinical studies:**
  - **Primary Pharmacology**

The IL-1 pathway contributes to local and systemic inflammation and is thought to play a role in inflammatory diseases. IL-1α/β blockade is known to affect innate immunity, neutrophilic inflammation, and downstream inflammatory cytokines such as IL-6 and IL-8. Lutikizumab, a DVD-Ig, is a unique molecule that specifically neutralizes both IL-1α and IL-1β. Based on the literature data and additional findings, there is a strong rationale for investigating lutikizumab in immune-mediated inflammatory diseases including HS.

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No dedicated nonclinical absorption, distribution, metabolism, excretion or drug-drug interaction studies have been conducted.

- **Toxicology**

Cynomolgus monkey was the only species utilized for toxicology studies based upon a lack of lutikizimab binding to IL-1 from dog, rabbit, rat or mouse. Lutikizumab demonstrates neutralizing activity against IL-1 from both humans and cynomolgus monkeys.

GLP-compliant 13- and 26-week cynomolgus monkey toxicology studies were conducted with lutikizumab. There were no adverse effects. Non-adverse effects were limited to mild SC injection site reactions. The NOAEL dose level was the highest dose level evaluated in each study.

Tissue Cross-Reactivity Studies

Tissue cross-reactivity studies were conducted with lutikizumab and cryopreserved tissues from humans and cynomolgus monkeys. Immunohistochemical staining patterns of lutikizumab in human and cynomolgus monkey TCR studies were similar between the two species and consistent with literature reports of IL-1 expression.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies of lutikizumab have not been conducted.

-No lutikizumab-dependent organ weight or histologic changes were observed among the reproductive organs of sexually mature animals utilized during the GLP-compliant 26-week monkey toxicology study..

Genotoxicity

Genotoxicity studies of lutikizumab have not been conducted.

Carcinogenicity

Carcinogenicity studies have not been conducted.

- **Summary of previous clinical studies:**

- All AbbVie-sponsored clinical investigations conducted with lutikizumab are listed in **the following table:**

Study Status	Study Number	Countries	Study Design	Primary Objectives	Study Status
M12-756/ Phase 1/ Completed	36/36: 28 lutikizumab 8 placebo	US	Randomized, double-blind, placebo-controlled, multiple ascending dose study in subjects with osteoarthritis of the knee; 0.3, 1, and 3mg/kg lutikizumab SC	Assess safety, tolerability, and pharmacokinetics	Lutikizumab did not show any consistent differentiation from placebo for PROs. Lutikizumab significantly reduced serum ANC and

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					serum levels of hsCRP, C1M, IL-1α, and IL-1β, and demonstrated a decreasing trend for serum concentrations of C3M and CRPM. Overall, multiple doses of lutikizumab (maximum dose of 3 mg/kg lutikizumab EOW for 4 doses total) were well tolerated in subjects with OA. Neutrophil data from the study suggest a dose-response relationship with lutikizumab administration and declines in ANC and WBC count.
M13-741/ Phase 2a/ Completed	347a/320: 262 lutikizumab 85 placebo	Australia, Canada, Denmark, France, Italy, Mexico, the Netherlands, Spain, UK, and US (including Puerto Rico)	Randomized, double-blind, parallel-group, placebo-controlled, 52-week study of 3 dose levels of lutikizumab in subjects with symptomatic, radiographic, and inflammatory knee OA;25, 100, and 200 mg lutikizumab SC	Evaluate efficacy of lutikizumab on OA knee pain, safety, and tolerability	The co-primary efficacy endpoint of pain improvement as measured by WOMAC pain scores in subjects with OA was achieved in the lutikizumab 100 mg group only; however, virtually all secondary endpoints related to pain/function and all co-primary and

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					secondary efficacy endpoints related to knee structure and disease modification were similar to placebo in all lutikizumab dose groups. Positive ADA titers detected in subjects treated with lutikizumab did not have a consistent or substantial impact on lutikizumab exposures. The TEAEs and laboratory findings are consistent with the known safety profile of the IL-1 inhibitor drug class established with other compounds in approved indications other than OA.
M14-171/ Phase 2a/ Completed	131b/120: 64 lutikizumab 67 placebo	Belgium, Denmark, France, the Netherlands, Switzerland, US	Randomized, double-blind, parallel-group, placebo-controlled, 26-week study of lutikizumab in subjects with erosive hand OA; 200 mg lutikizumab SC	Evaluate the effect of lutikizumab on pain due to erosive hand OA, safety, and tolerability	The effects of lutikizumab on reduction of pain, improvement in function, or overall improvement on the AUSCAN 3.1 did not yield statistically significant differences from placebo in subjects with erosive hand OA.

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					Lutikizumab serum concentrations attained steady state by Wk 6 visit, with approximately 2-fold accumulation compared to Wk 2 visit. The magnitude of ADA response was low and did not appear to impact the pharmacokinetic behavior of lutikizumab. The TEAEs and laboratory findings are consistent with the known safety profile of the IL-1 inhibitor drug class established with other compounds in approved indications other than OA.
M20-262/ Phase 2/ (Main Study) Completed	153/160 (Main): 113 lutikizumab 40 placebo	Australia, Canada, Germany, Greece, Japan, Puerto Rico, Spain, US	Randomized, Double-blind placebo-controlled study in subjects with **moderate** to **severe HS** who have failed anti-TNF therapy (Main Study)	Evaluate the safety and efficacy of lutikizumab in adult subjects with moderate to severe HS who failed anti- TNF Therapy (Main Study)	Main Study The analysis showed that subjects who received lutikizumab 300 mg SC EOW or 300 mg SC EW achieved higher response rates than placebo in the primary endpoint of HiSCR **at Week 16.** Subjects that received

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					lutikizumab 300 mg SC EOW and lutikizumab 300 mg SC EW achieved better efficacy of improved skin pain via the secondary endpoint of NRS30 at Week 16 and the additional efficacy endpoint of HiSCR 75 at Week 16 compared to placebo. Overall, lutikizumab 100 mg SC EOW group did not demonstrate better efficacy relative to the placebo group for the primary endpoint. Treatment with lutikizumab was generally safe and well-tolerated in this study.
M20-262/ Phase 2/ (Sub study) Ongoing	0/40	Australia, Canada, PR & US	Open-label study in subjects with moderate to severe HS who are naïve to biologic therapy (Sub study)	Evaluate the safety and efficacy of lutikizumab in adult subjects with moderate to severe HS who are naïve to biologic therapy (Sub study)	Sub study Data are not available for this ongoing study.
M24-465/ Phase 1 / Completed	50/50 50 lutikizumab	US	Single dose, open-label, randomized, two parallel arms multi-center study in healthy	To compare the bioavailability of two different formulations of lutikizumab, and to assess adverse events	Data are not available for this study.

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			adult Han Chinese volunteers	(AEs) and how lutikizumab moves through the body in healthy Chinese participants.	
M23-703/ Ph2b / Ongoing	0/200	TBD	Multicenter, randomized, double-blind, double-dummy, dose ranging study	To evaluate the safety and efficacy of Lutikizumab when compared to adalimumab in adult subjects with moderately to severely active UC	Data are not available for this planned study.
M20-465 Phase 3/ Ongoing	0/ 1280	TBD	Multicenter, randomized, double-blind placebo controlled Study	Study to evaluate the efficacy and safety of lutikizumab in adult and adolescent subjects with moderate to severe HS	Data are not available for this ongoing study
M24-922 Phase 2/ Ongoing	0/60	US	Multicenter, open label study	To assess molecular changes in adult participants with moderate to severe HS or with moderate to severe AD.	Data are not available for this ongoing study.

- **Pharmacokinetics in Human**

- **Phase 1 Studies**

As of 29 February 2024, the safety, tolerability, and pharmacokinetics of lutikizumab have been evaluated in multiple Phase 1 studies. **More than 50 healthy volunteers and 28 subjects** with **knee OA** received at **least 1 dose of lutikizumab via SC administration** during Phase 1 studies.

Study M12-756: Multiple Ascending Dose Study of Lutikizumab in Subjects with Osteoarthritis of the Knee

Study M12-756 was a randomized, double-blind, placebo-controlled, multiple ascending dose study conducted in 36 subjects with mild to moderate knee osteoarthritis who were otherwise healthy. Subjects aged 40-70 years were randomized into four subcutaneous dose groups, with 7 subjects receiving lutikizumab and 2 receiving placebo per group. The study was not designed to evaluate efficacy.

Treatment with lutikizumab reduced absolute neutrophil count and several inflammatory biomarkers, including hsCRP, C1M, IL-1α, and IL-1β, while C3M and CRPM showed decreasing trends. These biomarker changes suggest target engagement and an anti-inflammatory effect.

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Study M24-465: Healthy Subjects to Evaluate the Relative Bioavailability of Two Lutikizumab Formulations and to Evaluate Lutikizumab Pharmacokinetics, Safety, and Tolerability in Healthy Chinese Subjects

The purpose of this study is to compare the bioavailability of two different formulations of lutikizumab, and to assess adverse events (AEs) and how lutikizumab moves through the body in 50 healthy Chinese participants.

- **Phase 2 Studies**

-Serum lutikizumab concentration data are available from two completed Phase 2a studies in subjects with OA and one completed Phase 2 b study in subjects with moderate to severe HS. In the Phase 2 studies, lutikizumab was administered as multiple SC doses.

- **Drug-Drug Interactions**

-No drug-drug interaction studies have been conducted for lutikizumab. As a recombinant DVD-Ig antibody, Lutikizumab is not expected to undergo hepatic metabolism or renal elimination and therefore is not expected to be a victim of drug-drug interactions with inhibitors/inducers of drug metabolizing enzymes.

-Treatment with lutikizumab would lead to reduced chronic inflammation and decrease in pro-inflammatory cytokines such as IL-1 and IL-6, which may result in increased level of metabolism and decrease in drug exposures for concomitant medications that are CYP substrates. Therefore, there is a theoretical risk for a perpetrator effect of lutikizumab on concomitant medications that are CYP substrate

- **Immunogenicity**

The magnitude of ADA to lutkizumab was low to moderate in OA or HS subjects, and there was no clear correlation between ADA titer incidence and lutikizumab dose. For most subjects, antibodies to lutikizumab, including NAb, were of low titer and not associated with changes to lutikizumab serum concentrations compared to ADA-negative subjects.

- **Safety**

No new or unexpected significant safety concerns have been identified for lutikizumab. No pregnancies or subject deaths occurred during any of the studies. No product complaints that have an impact on patient safety have been identified for lutikizumab in the individual clinical studies.

-Summary of the ADRs for lutikizumab based on the Phase 1 studies (M12-755, M12-756, M14-257, and M12-934), Phase 2a OA studies (Study M13-741 and Study M14-171) and on the Phase 2 M20-262 Main Study is presented by MedDRA system organ classes/preferred terms, with frequency calculations including both related and not related AEs.

Frequencies are defined as:

• Very Common (≥ 1/10 [≥ 10%]);
• Common (≥ 1/100 to < 1/10 [≥ 1% to < 10%]);
• Uncommon (≥ 1/1000 to < 1/100 [≥ 0.1% to < 1%]);

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• Rare (≥ 1/10,000 to < 1/1,000 [≥ 0.01% to < 0.1%]);
• Very Rare (< 1/10,000 [< 0.01%]).

-The most frequently reported (≥ 5%) **AEs and serious adverse events (SAEs)** considered **not related to lutikizumab** from the Phase 1 and Phase 2 studies.

Most Frequently Reported (≥ 5%) Treatment-Emergent Adverse Events Not Related to Lutikizumab in Studies M12-755, M12-756, M14-257, M12-934, M13-741, M14-171, M20-262 Main Study.

-Eight Suspected Unexpected Serious Adverse Reaction (SUSAR) events have been reported with lutikizumab treatment during clinical development in the OA indication and one in the HS indication.

- **Phase 2a Studies in Osteoarthritis**

To date**, 326 subjects** with knee or hand OA have received **at least 1 dose** of lutikizumab **via SC** administration in Phase 2a studies.

1)Study M13-741: Multiple-Dose, Placebo-Controlled, Safety and Efficacy Study of Lutikizumab in Subjects with Osteoarthritis of the Knee

Study M13-741 was a Phase 2a, multicenter, randomized, double-blind, placebo-controlled trial evaluating the safety, tolerability, efficacy, and pharmacodynamic effects of lutikizumab in patients with knee osteoarthritis. A total of 350 subjects were enrolled, and 347 received subcutaneous lutikizumab (25 mg, 100 mg, or 200 mg) or placebo every two weeks for 52 weeks. Overall, 262 subjects completed the study, and the most common reason for discontinuation was adverse events (AEs).

Most subjects experienced at least one treatment-emergent AE, with drug-related AEs reported more frequently in the lutikizumab group (58.0%) than in the placebo group (36.5%). However, discontinuations due to AEs were slightly lower in the lutikizumab group. The most commonly reported AEs included headache, arthralgia, neutropenia, nasopharyngitis, back pain, decreased neutrophil count, upper respiratory tract infection, and injection site reactions.

Serious adverse events (SAEs) occurred at similar rates in the lutikizumab and placebo groups, with the most frequent events including falls, cholecystitis, fractures, and traffic accidents. A few SAEs were considered possibly related to treatment, including pneumonia, colon adenoma, and invasive ductal breast carcinoma in the lutikizumab group.

Neutropenia occurred more frequently in the lutikizumab groups in a dose-dependent manner and was considered drug-related, with some cases leading to treatment discontinuation. Injection site reactions and hypersensitivity events were also more common with lutikizumab and increased with higher doses.

There were no notable differences between groups in rates of infections, serious infections, lipid increases, thrombocytopenia, or hepatic events, and no cases of active or reactivated tuberculosis were reported. No deaths or pregnancies occurred during the study.

A higher number of malignancies was observed in the lutikizumab group compared with placebo, though most were not considered related to treatment, except for one case of invasive ductal breast carcinoma. One major adverse cardiac event (cerebral hemorrhage due to a bicycle accident) occurred but was not considered related to the study drug.

Potentially Clinically Significant Laboratory Results:

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Post-baseline neutrophil counts were assessed using NCI CTCAE criteria, and most potentially clinically significant laboratory abnormalities (Grade ≥2) were transient and resolved during treatment.

Neutropenia occurred more frequently in the lutikizumab group than in the placebo group, with Grade 2 neutropenia reported in 26.7% of lutikizumab-treated subjects compared with 3.5% in placebo. Grade 3 neutropenia occurred in 2.7% of lutikizumab-treated subjects and in none of the placebo subjects, with incidence increasing in a dose-dependent manner. No Grade 4 neutropenia was observed.

Compared with placebo, a higher proportion of subjects receiving lutikizumab experienced decreases in WBC count and neutrophils and increases in total cholesterol, with WBC and neutrophil reductions showing a dose-dependent trend. However, no Grade 4 decreases in WBC or neutrophils and no Grade ≥3 increases in cholesterol were reported.

Efficacy Conclusions:

The primary efficacy endpoint of WOMAC pain in the index knee at Week 16 **was achieved only in the lutikizumab 100 mg dose group**.

2)Study M14-171: Multiple-Dose, Placebo-Controlled, Safety and Efficacy Study of Lutikizumab in Subjects with Erosive Osteoarthritis of the Hand

Study M14-171 was a Phase 2a, multicenter, randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of lutikizumab (200 mg every two weeks) in patients with erosive hand osteoarthritis over 24 weeks. A total of 132 subjects were enrolled, with 131 receiving at least one dose of either lutikizumab or placebo, and 110 subjects completed the study.

Most subjects in both groups experienced at least one treatment-emergent adverse event (AE), with drug-related AEs reported more frequently in the lutikizumab group. Serious adverse events (SAEs) occurred in a small number of subjects in both groups; in the lutikizumab group, two SAEs (discolored feces and decreased hemoglobin) in one subject were considered related to the study drug.

Discontinuations due to AEs occurred in 7.8% of subjects receiving lutikizumab and 3.0% receiving placebo. In the lutikizumab group, discontinuations were mainly due to neutropenia and injection site reactions (including rash, erythema, pruritus, and urticaria). Injection site reactions were more frequent with lutikizumab than with placebo.

No serious infections, deaths, pregnancies, or cases of active or reactivated tuberculosis were reported. Additionally, no differences between treatment groups were observed in the incidence of hypersensitivity reactions, infections, or lipid level increases.

Potentially Clinically Significant Laboratory Results:

Post-baseline neutrophil counts were graded according to NCI CTCAE criteria. For the lutikizumab treatment group, 9 subjects (14.1%) had Grade 2 neutropenia based on laboratory data, 3 subjects (4.7%) had Grade 3 neutropenia, and no subjects who took lutikizumab had Grade 4 neutropenia. No subjects in the placebo treatment group had Grade 2, 3, or 4 neutropenia. Five subjects (7.9%) had Grade ≥ 2 neutropenia on at least 2 consecutive post-baseline visits for lutikizumab.

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Post-baseline neutrophil counts were evaluated using NCI CTCAE criteria. In the lutikizumab group, 14.1% of subjects experienced Grade 2 neutropenia and 4.7% experienced Grade 3 neutropenia, while no Grade 4 neutropenia was reported. No neutropenia events occurred in the placebo group. Additionally, 7.9% of subjects receiving lutikizumab had Grade ≥2 neutropenia on at least two consecutive visits.

- **Phase 2 Study in Hidradenitis Suppurativa**

Study M20-262 (Main Study): Phase 2 Study in Subjects with HS

This Phase 2, multicenter, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of lutikizumab in adults with moderate to severe hidradenitis suppurativa (HS) who had failed anti-TNF therapy. A total of 153 subjects were randomized, and 113 received lutikizumab (100 mg or 300 mg every other week, or 300 mg weekly) or placebo. The main study has been completed, while a substudy remains ongoing.

- **Protocol:** A Phase 3 Multicenter, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Efficacy and Safety of Lutikizumab in Adult and Adolescent Subjects with Moderate to Severe Hidradenitis Suppurativa

Phase: III

Objective(s):

Period 1	Period 2
The primary objective is to assess the efficacy and safety of Lutikizumab versus placebo for the treatment of the signs and symptoms of moderate to severe HS in subjects 12 years of age and older	**The primary objectives are:** • To assess the efficacy and safety of continuing Lutikizumab dosing in Period 1 or switching to a lower dose in subjects who received Lutikizumab in Period 1. • To evaluate the benefit of switching to Lutikizumab in subjects who received placebo in Period 1.

Study End point:

Primary Endpoint

The primary endpoint is the achievement of HiSCR 75 at Week 16. HiSCR 75 is defined as at least a 75% reduction from baseline in the total AN count, with no increase in abscess count and no increase in draining fistula count relative to baseline.

Secondary Endpoints

Ranked Secondary Endpoints

1. Achievement of NRS30 (at least a 30% reduction and at least 2-units reduction from Baseline in the Patient's Global Assessment of HS-related skin pain NRS) at Week 8 among subjects with NRS ≥ 3 at Baseline. The NRS30 is based on worst skin pain in a 24-hour recall period (maximal daily pain);

2. Change from Baseline in DLQI at Week 16;

3. Change from Baseline in HSIA at Week 16;

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4. Change from Baseline in HSSA Worst Drainage Score at Week 16;
5. Change from Baseline in Draining Fistula at Week 16;
6. Achievement of HiSCR 90 (at least a 90% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline) at Week 16;
7. Change from Baseline in the Patient's Global Assessment of HS-related Skin Pain (NRS) at Week 8;
8. Change from Baseline in HSSA at Week 16;
9. Change from Baseline in HS-related odor (smell), based on HSSA Question 8, at Week 16;
10. Occurrence of HS flare, defined as at least one occurrence of a ≥ 25% increase in AN count with a minimum absolute increase of 2 relative to Baseline during the first 16 weeks (Period 1).

Safety Endpoints

Safety will be assessed by AE monitoring, physical examination, vital signs, chest x-ray, and clinical laboratory testing during the study. Laboratory assessments will include pregnancy assessments, hematologic parameters, chemistry, liver function tests, lipid parameters, and urine analysis.

Pharmacokinetic and Immunogenicity Endpoints

Serum Lutikizumab concentrations, ADA, and NAb will be determined from blood samples.

Rationale:

-HS is a debilitating inflammatory skin disease with a characteristic clinical presentation of recurrent or chronic painful, suppurating lesions that most commonly appear in the axilla, inguinal, and anogenital regions. The estimated prevalence of HS varies between < 1% and 4%. Important differential diagnoses of HS are furuncles, carbuncles, abscesses, cutaneous Crohn's disease, and acne. It is a difficult condition to diagnose for health care providers without in-depth knowledge of the disease. Therefore, there is a significant delay (7.2 years on average) in establishing the diagnosis of HS after its initial presentation.
HS lesions (i.e., nodules, abscesses, and sinuses) are characterized by painful lesions located in the intertriginous areas, which can be malodorous and have purulent discharge. This constellation results in substantial disability and social stigma of the patients and a profound impact on the quality of life. Depression, anxiety, and an increased suicide risk may be seen in patients with HS, and the disease may have an adverse influence on a patient's sexual health. HS is associated with comorbidities such as obesity, metabolic syndrome, diabetes, arthritis, Crohn's disease, and polycystic ovarian syndrome.
-One of 2 approved treatment options for patients with moderate to severe HS is adalimumab (Humira®), a TNF-α inhibitor. The results from two Phase 3, multicenter, double-blind, placebo-controlled studies (PIONEER I and PIONEER II) showed approximately 42% and 59% of subjects achieved HiSCR 50 at Week12 with adalimumab treatment, respectively, versus 26% and 28% with placebo. HiSCR 50 is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline. The other option is Secukinumab (Cosentyx®), an IL-17 inhibitor, was recently approved based on results from two Phase 3, multicenter, double-blind, placebo-controlled studies (Sunshine and Sunrise). Approximately 42% and 46% of subjects, respectively, achieved HiSCR 50 at Week 16 with secukinumab treatment every 4 weeks versus 34% and 31% with placebo.

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In the context of these limited HS-approved treatment options, additional therapies are still needed to address the high unmet need for new safe and efficacious HS therapies.

Based on published literature and internal unpublished analyses, both IL-1α and IL-1β are upregulated in skin lesions of patients with HS. In HS, the IL-1 pathway induces IL-6 expression, and in HS patients, IL-1β and IL-6 are systemically elevated compared to healthy controls3 and correlate with clinical inflammatory disease activity.23 These results suggest that targeted inhibition of IL-1-mediated inflammation may improve the signs and symptoms of HS.

Lutikizumab, a DVD-Ig, specifically neutralizes both IL-1α and IL-1β without interfering with IL-1RA–mediated regulatory functions in the IL-1 pathway. Study M20-262 is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled, dose ranging study which evaluated the efficacy and safety of lutikizumab in adult subjects with moderate to severe HS who failed anti-TNF therapy in the Main Study. The results of the Main Study demonstrated the efficacy of lutikizumab in achieving HiSCR 50 after 16 weeks of treatment in subjects with moderate to severe HS. Lutikizumab also achieved improved skin pain via the secondary endpoint of NRS30 and the additional efficacy endpoint of HiSCR 75, a higher threshold of HS clinical response.

--Additionally, lutikizumab was generally safe and well tolerated at all doses as assessed by frequency of AEs, including SAEs, AESIs, and clinical laboratory values. No new safety concerns for lutikizumab treatment were identified. Based on the literature data and work at AbbVie, there is a strong rationale to support the continued investigation of lutikizumab in the treatment of HS.

Benefits and Risks to Subjects

Despite the clinical benefit offered by adalimumab and secukinumab therapies to patients with moderate to severe HS, approximately 50% of patients will not achieve response with therapy.

Additionally, secukinumab has only been approved in adults. Therefore, there remains a significant unmet medical need for effective and safe therapies for patients with moderate to severe HS. Data suggest that blocking the IL-1 pathway could provide potential therapeutic benefit to patients with HS. Inhibition of both IL-1α and IL-1β is expected to interrupt the inflammatory cascade observed in HS. Furthermore, positive results across multiple efficacy endpoints at Week 16 and supportive safety data of the Phase 2 Study M20-262 support further investigation of lutikizumab as a treatment for patients with moderate to severe HS.

Lutikizumab has been generally safe and well tolerated at all doses across clinical trials, including 3 Phase 2 studies (subjects with knee osteoarthritis, subjects with erosive hand osteoarthritis, and subjects with HS). The ADRs from those studies, including neutropenia, neutrophil count decrease, pruritus, nausea, and injection-site reactions, are consistent with the known safety profile of the IL-1 Inhibitor drug class. Several biologic agents that target the IL-1 pathway have been evaluated in humans for different disease states, and some of these approaches (anakinra, rilonacept, and canakinumab) are currently approved for the treatment of several autoimmune diseases.

Design:

This is a pivotal Phase 3, global, randomized, double-blinded, placebo-controlled, multicenter study to

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evaluate efficacy and safety of Lutikizumab in subjects 12 years of age and older with moderate to severe HS. Subjects naïve to biologic therapy (bio-naïve) for HS and those who have been treated with a prior biologic therapy for HS will be eligible.
The schematic of the study is shown in **the following figure:**

- ***Recommendation &/ or*** **Questions & Answers: NA**

- **Abbreviation:**

µg/mL: Microgram per Milliliter
mg/kg: Milligram per Kilogram
mg·hr/mL: Milligram-Hour per Milliliter
ng: Nanogram
nM: Nanomolar
pM: Picomolar
ADA: Anti-Drug Antibodies
ADRs: Adverse Drug Reactions
AE: Adverse Event
AESIs: Adverse Events of Special Interest
ANC: Absolute Neutrophil Count
AUSCAN: Australian/Canadian Osteoarthritis Hand Index
C1M: Matrix Metalloproteinase-Derived Type I Collagen Neoepitope
C3M: Matrix Metalloproteinase-Derived Type III Collagen Neoepitope
CRPM: C-Reactive Protein Matrix Metalloproteinase
CRO: Contract Research Organization
CT: Clinical Trial
DLQI: Dermatology Life Quality Index
DVD-Ig: Dual-Variable Domain Immunoglobulin
EOW: Every Other Week
EW: Every Week
GLP: Good Laboratory Practice
HiSCR50: Hidradenitis Suppurativa Clinical Response 50
HS: Hidradenitis Suppurativa
HSIA: Hidradenitis Suppurativa Investigator's Assessment
IB: Investigator’s Brochure
IL: Interleukin
IL-1: Interleukin-1
IL-1α: Interleukin-1 Alpha
IL-1β: Interleukin-1 Beta
IL-1RA: Interleukin-1 Receptor Antagonist
IL-1RI: Interleukin-1 Receptor Type I

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IL-6: Interleukin-6
MedDRA: Medical Dictionary for Regulatory Activities
NA: Not Applicable
NAB: Neutralizing Antibodies
NCI: National Cancer Institute
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL: No-Observed-Adverse-Effect Level
NRS30: Numerical Rating Scale (30% Reduction)
OA: Osteoarthritis
PI: Principal Investigator
SAEs: Serious Adverse Event(s)
SC: Subcutaneous
SUSAR: Suspected Unexpected Serious Adverse Reaction
TEAE: Treatment-Emergent Adverse Event
WBC: White Blood Cell
Wk: Week
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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