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# Advancements In Novel Therapeutics For Chronic Spontaneous Urticaria

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Abbreviations:

- BTK: Bruton tyrosine kinase
- CIndU: chronic inducible urticaria
- CSU: chronic spontaneous urticaria

- CU: chronic urticaria
- FcεRI: high-affinity IgE receptor
- FDA: Food and Drug Administration
- fgAH: first-generation antihistamine
- IL: interleukin
- ISS7: itch severity score over 7 days
- LTRA: leukotriene receptor antagonist
- MRGPRX2: Mas-related G-protein-coupled receptor X2
- PROMs: patient-reported outcome measures
- QOL: quality of life
- sgAH: second-generation antihistamines
- Siglec: sialic acid-binding immunoglobulin-like lectin
- TNF-α: tumor necrosis factor
- TPO: IgG anti-thyroid peroxidase antibodies
- TSLP: thymic stromal lymphopoietin
- UAS: urticaria activity score
- UAS7: urticaria activity score over 7 days
- $UAS7_{TD}$: urticaria activity score twice daily over 7 days
- UCT: urticaria control test
- UCT7: urticaria control test over 7-day recall period

**Abstract:**

Chronic urticaria (CU) is defined by pruritic wheals with or without angioedema, associated with severe itch, which persist for greater than 6 weeks. Lesions move from one part of the body to another and generally are evanescent, lasting less than 24 hours. The global prevalence of the disease ranges from 0.5 - 5%, and is correlated with an annual economic burden over $200 million in the United States. CU can be further divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). Whereas CSU has no identifiable trigger, CIndU can be provoked by both physical and non-physical stimuli. As many as 7 - 30% of CU patients can have both types. Mast cells are the major effector cells in the pathogenesis of CU. When activated, mast cells characteristically release bioactive mediators including histamine that bind to specific receptors causing vasodilation and extravasation of fluid from the blood vasculature. This causes the characteristic wheals and itch. However, the pathophysiology of CU is much more complex, involving many mast cell surface receptors, cytokines, and cell activation pathways which are targets for many of the currently available and investigational therapies. Studies have demonstrated that CU causes a significant amount of distress and disruption to patients' daily lives that can be evaluated using validated patient-reported outcomes measures (PROMS). In this review, we will review CU epidemiology, pathophysiology, subtypes and diagnosis with discuss current and novel therapies.

Key Words: Mast cells, chronic urticaria, chronic inducible urticaria, patient reported outcome measures, pathophysiology, novel therapies,

**Introduction:**

Chronic spontaneous urticaria (CSU) is defined by pruritic wheals with or without angioedema, associated with severe itch, which persist for greater than 6 weeks. Lesions migrate from one part of the body to another and are evanescent, lasting mostly less than 24 hours.[1,2] Chronic spontaneous urticaria can be associated with chronic inducible urticaria (CIndU).[3] Whereas CSU has no identifiable trigger, CIndU can be induced by both physical or non-physical triggers.[4] As many as 7 - 30% of CSU patients can have both types.[5, 6] Chronic spontaneous urticaria has a global prevalence of 0.5-5%.[1-3, 7, 8]. The prevalence of CSU has been estimated to be rising two- to tenfold.[5] Women tend to be more commonly affected than men with median onset age of 40 years; however, the age of onset differs between countries and CSU also affects children.[5, 8-10] A study by Fricke et al. found that the point prevalence of CSU was highest in Latin America and Asia and lowest in Northern America.[9]

Chronic spontaneous urticaria is associated with a significant annual economic burden of greater than $200 million in the United States or approximately greater than $2000 in annual costs per patient.[1, 3, 11] The cost of CSU to our healthcare system which includes direct and indirect costs such as medications, outpatient visits, emergency department visits, hospital admissions, and work absences approaches the annual outpatient costs for hypertension, diabetes, and other chronic skin conditions like bullous diseases and vitiligo.[3, 11] Compared to healthy individuals, CSU patients have a higher incidence ratio of healthcare utilization: 1.71 inpatient, 2.39 emergency, 2.07 outpatient visits per year.[5]

The pathophysiology of CSU is complex, involving many mast cell surface receptors, cytokines, and cell activation pathways which are targets for many of the currently available and investigational therapies for this condition.[6, 12-14] Previous studies have found that only

approximately 40% of patients respond to monotherapy with H1-antihistamines or combinations of H1-antihistamines, H2-antihistamines and leukotriene modifying agents.[1] With the introduction of the biologic omalizumab, approved for the treatment of CSU, approximately 45% of patients previously uncontrolled on H1-antihistamine achieved complete control (UAS7=0). An additional 45% were reported to be partially controlled (UAS7≤6).[15-19] Our understanding of the pathogenesis of CSU has improved substantially in the biologic era as we now have been able to better characterize responder and non-responder patients to omalizumab. Studies suggest that CSU patients with high C-reactive protein and d-dimer are less responsive to H1-antihistamines and patients with low total IgE, high levels of IgG anti-thyroid peroxidase antibodies (TPO), and high CU index, a positive basophil activation test that acts as a surrogate marker for autoantibodies targeting high affinity IgE receptors (FcER1alpha subunit), are unresponsive or partially responsive to omalizumab.[20, 21] Recently, TPO was reported to have the best predictive value among these biomarkers for predicting a poor response to omalizumab.[21] Thus, there is a gap in therapy for subtypes of patients not completely controlled on existing CSU treatments, necessitating the development of novel therapies for treatment of these more difficult to treat patients. In this review, we will provide an overview of the currently used advanced therapies for CSU and provide a perspective on the therapies that are being repurposed or are being newly developed for the treatment of CSU.

**Pathophysiology of CSU**

Mast cells are derived from the myeloid cell line. Activation of mast cells leads to the release of bioactive mediators including histamine, prostaglandin, leukotrienes and platelet-activating factor among others, which are essential for the development of CSU wheals and itch with or without angioedema.[22] There are several CSU phenotypes associated with defined

endotypes that have been proposed.[22-24] These include H1 anti-histamine responsive CSU with or without angioedema, type I autoallergic CSU and type IIb autoimmune urticaria. Type I autoallergic CSU is characterized by IgE antibodies targeting self-antigens, whereas type IIb autoimmune CSU involves IgG antibodies targeting the high affinity IgE receptor, FcεRIα subunit, or IgE bound to these receptors on mast cells.[2, 6, 7, 13, 22-24]. Interestingly, CSU patients can manifest with either endotype or with both **(Figure 1).**[24] Patients with type I autoallergic CSU tend to be more responsive to medical treatment, whereas patients with type IIb autoimmune CSU are more resistant and often difficult to manage, being a target for novel therapies.[24]

[**INSERT FIGURE 1 HERE]**

**Mast cell activation and mediator release**

This occurs through exocytosis of granules that fuse to the cell membrane or through a general secretory mechanism called piecemeal degranulation, which is a unique ultrastructural pattern of cell secretion, where granules release their contents but do not fuse with other granules or to the cell membrane (**Figure 2**).[25-28] Different activating stimuli can elicit different secretory responses from mast cells that exhibit unique dynamics associated with distinct mast cell dependent inflammation.[29] For example, neuropeptides like substance P, complement anaphylatoxins C3a and C5a, and endothelin 1, have been shown to rapidly induce human mast cells to release granules.[29] As illustrated in Figure 2, there are now many well identified surface receptors that have been characterized resulting in the development and investigation of several novel molecules for CSU treatment.[30]

[**INSERT FIGURE 2 HERE]**

Basophils, which belong to the granulocyte family of cells, are another key effector cell involved in CSU, as they have been found to be present in the biopsies of urticarial wheals. Similar to mast cells, basophils also have various surface receptors including FcεRI and C5aR that, when activated, can lead to release of cytokines and bioactive mediators like histamine and leukotrienes.[22, 27, 30]

Activation of mast cells and basophils initiate de novo synthesis and release of cytokines and chemokines, resulting of inflammatory cells into the epidermis for patients with isolated CSU and into the deeper dermis in CSU patients with angioedema. These inflammatory cytokines along with released bioactive mediators lead to vasodilation and increased vascular permeability resulting in extravasation of fluid manifesting as wheal, flare and itch, the three classic characteristics of CSU.[27] Skin biopsy samples from CSU patients have shown CD4+ T cells, monocytes, and a mixture of neutrophils, eosinophils, and basophils along with their associated cytokines including IL-4, IL-5, IL-6 IL-33, IL-25, and thymic stromal lymphopoietin (TSLP). Biopsies obtained from CSU patients typically exhibit lymphocytes with either primarily eosinophils but neutrophils or a mixture of eosinophils and neutrophils can be observed. Patients whose biopsies consist predominantly of neutrophils or a mixture of eosinophils and neutrophils tend to be more refractory to treatment with H1-antihistamines as this histologic pattern has been associated with autoimmune urticaria.[28, 31-35]

**Management of CSU**

The most recent international guidelines were published in 2022 are currently being updated for 2024 whereas the US Guidelines last published in 2014 arealso currently being updated as a GRADE guideline (Figure 3).[36]

[**INSERT FIGURE 3 HERE]**

CSU management also includes periodic monitoring of urticaria control and severity, together with patient satisfaction and side effects evaluation.[37]. The World Allergy Organization has recently proposed CSU remission definition as total resolution of urticaria signs and symptoms without pharmacotherapy for at least 6 months; a therapeutic de-escalation scheme has been suggested.[38] Step one therapy which includes updosing second generation $H_1$-antihistamines up to 4 times the FDA approved dose as well as alternative therapies like H2-antihistamines and leukotriene receptor antagonists included as first line treatments in the US 2014 CSU guidelines and in the "Alternative treatment" appendix in the International CSU Guidelines have been reviewed previously.[36, 37, 39] **Table 1 and Table 2** summarize the completed, terminated and ongoing biologic and small molecule studies for CSU and CindU, respectively, since the development of omalizumab.

**IgE Targeted Therapies:**

Omalizumab is a monoclonal antibody that binds to free IgE and thus, prevents binding to FcεRI. Omalizumab has also been found to downregulate the number of FcεRI receptors on mast cells and basophils.40 Clinical trials have demonstrated the clinical benefit of omalizumab in CSU.[17, 41] The standard dose is 300mg every 4 weeks; however, several studies have shown some patients only responded after dosing was increased to 600mg every 2 weeks.[42-47]. These higher doses can provide clinical benefits in 61% of patients with insufficient response to the standard dose.[42] As mentioned earlier, the controversy regarding the utility of biomarkers characterizing severity of CSU [19] or as predictors for response to H1-antihistamines or omalizumab remains unresolved [21]. Although patients with low total IgE, high thyroid autoantibodies and antibodies targeting high affinity IgE receptors (FcER1alpha

subunit) have been associated with partial or poor responders to omalizumab, in a recent study only TPO was predictive of a poor response to omalizumab.[21]

Ligelizumab is an anti-IgE monoclonal antibody similar to omalizumab but has 40 to 50 times higher affinity for IgE.[6] A phase 2b study showed that ligelizumab was more effective than omalizumab.[48] Subsequent phase 3 PEARL studies investigated 70mg and 120mg doses of ligelizumab administered every 4 weeks to patients at least 12 years of age for 52 weeks.[49] The study drug was compared to placebo and 300mg omalizumab. Both doses of ligelizumab demonstrated superiority compared to placebo at week 12 but unlike phase 2b studies ligelizumab was not more effective than omalizumab. Adverse events included injection site reactions, cardiovascular events such as non-serious tachycardia, and hypersensitivity reactions.[49] Development of this drug was discontinued since it did not show superiority to omalizumab in the phase 3 studies.

Recently two double-blind, randomized, active-controlled Phase 3, 12 week studies (NCT04426890) were conducted comparing omalizumab to the biosimilar CT-P39 in patients with CSU unresponsive to H1-antihistamines.[50] In study one, omalizumab naïve patients received either 150mg or 300mg doses of omalizumab compared to 150mg or 300mg doses of CT-P39 and in study 2 patients on omalizumab 300mg were randomized to receive CT-P39 300mg or omalizumab 300mg. Both studies demonstrated equivalent efficacy and safety between omalizumab and the omalizumab biosimilar, CT-P39.[50]

**Immunosuppressive Therapies:**

Cyclosporine is a calcineurin inhibitor that can downregulate the activation of T cells and production of inflammatory cytokines such as IL-2, IL-3, IL-4, and TNF-α. .[51] Cyclosporine can also act directly on mast cells and basophils by inhibiting histamine release.[52] Studies

have shown that cyclosporine is an effective treatment for CSU that is refractory to antihistamines.[51-54] A meta-analysis by Kulthanan et. al found a 73% response rate with 12-week use of cyclosporine but a clinical response can be seen as early as one month.[51] Dosing can range from 1 – 5 mg/kg/d.[51] Adverse effects include elevated creatinine, hypertension, gastrointestinal symptoms, headache, paresthesia, among others which tend to be dose- and duration-dependent.[54-59] Increased risk of skin malignancies have been found to occur with cyclosporine use in transplant recipients.[60] However, when observing patients on cyclosporine therapy for dermatologic conditions, which usually require lower doses and shorter durations, Muellenhoff and Koo found no increased risk of skin cancer in these patients.[61] A 3-6 month trial of cyclosporin is usually sufficient to see an effective response and if there is none then should be discontinued. In contrast, if there is a good clinical response, it is advisable to step down to identify the lowest effective dose and if still controlled, then discontinued to see if the patient is in remission as prolonged use carries an increased risk of nephrotoxicity.[57,58]

Other immunosuppressants that have been used to treat refractory CSU include tacrolimus, mycophenolate, methotrexate, and sirolimus.[62-65] Anti-inflammatory agents that have been used for CSU include dapsone, sulfasalazine, hydroxychloroquine, and colchicine.[1] Case studies and retrospective reviews have commented on the utility of these agents which can be trialed if omalizumab and cyclosporine are ineffective or intolerable.[66-69] One meta-analysis reported that hydroxychloroquine (SMD, -1.00 [-1.61 to -0.39]), 72 mg ligelizumab (SMD, -0.66 [-0.96 to -0.35]), 240 mg ligelizumab (SMD, -0.67 [-0.98 to -0.37]), and 300 mg omalizumab (SMD, -0.53 [-0.67 to -0.39]) significantly improved health related quality of life to a moderate effect but the use of hydroxychloroquine appeared limited by higher risk patients due poor acceptability of the treatment.[70]

**Cytokine Targeted Therapies:**

***IL-4/IL-13:***

Dupilumab is a monoclonal antibody that binds to IL-4α receptor and blocks IL-4 and IL-13 signaling. It is currently approved for various allergic conditions, such as atopic dermatitis, asthma, nasal polyposis, and eosinophilic esophagitis.[6] Two phase 3, randomized, placebo-controlled, double-blind trials, CUPID A and B, compared the use of dupilumab in omalizumab-naive and intolerant or incomplete omalizumab responders, respectively.[71] End points measured were Urticaria Activity Score over 7 days (UAS7) and Itch Severity Score over 7 days (ISS7). The studies found that dupilumab reduced severity of itch and hives in omalizumab-naïve, patients but not in omalizumab-intolerant or incomplete responders.[71] A subsequent study, CUPID C, designed similarly to CUPID A, was conducted to assess efficacy and safety of dupilumab compared to placebo.[71,72] The LIBERTY-CUPID C randomized trial evaluated dupilumab as an add-on to second generation anti-histamines (SGAH) compared with SGAH alone in 151 omalizumab naïve patients with CSU of ≥ 6 years of age who remained symptomatic despite H1-antihistamine use. This study confirmed the CUPID A study results as it found that 30% of dupilumab-treated patients had a complete response at 24 weeks compared with 18% on placebo ($p = 0.02$) with a good safety profile.[72] Although the initial CUPID B study found dupilumab didn't outperform omalizumab, there are no head-to-head comparisons of these agents. However, there are case series of omalizumab non-responders, responding to dupilumab.[73] Dupilumab is approved for CSU in Japan and Brazil and has recently been approved by the FDA in the United States for patients 12 years and older who remain symptomatic despite H1 antihistamine treatment. Its approval in Europe is still pending. .

With the advent of dupilumab's approval for CSU, clinicians will have to determine whether to initially start omalizumab or dupilumab for patients unresponsive to H1-antihistamines. In our limited experience, the selection of one agent over the other has depended on patient comorbid conditions such as concomitant atopic dermatitis or prurigo nodularis or the presence of biomarkers such as high TPO and autoantibodies targeting FcER1alpha subunit or low total IgE which would all favor dupilumab over omalizumab. However, real world experience with these agents will no doubt provide greater insights on their optimal use in patients with different phenotype/endotype characteristics.

***TSLP:***

Alarmins IL-25, IL-33 and TSLP are known to be increased in the dermis of CSU patients.[33] Tezepelumab, an anti-TSLP mAb, has shown efficacy in the treatment of patients with asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)..[74,75] A recent phase IIb study evaluating tezepelumab in antihistamine refractory, anti-IgE naïve CSU did not meet the primary endpoint of UAS7 from baseline to 16 weeks, although there was numeric improvement in UAS7 scores that was sustained for 16 weeks not seen with omalizumab.[76,77]

***IL-5/IL-5R:***

Anti-IL-5 targeted therapies have also been largely ineffective for management of CSU. Despite an open label study demonstrating statistically significant reduction in UAS7 for benralizumab, an anti-IL-5 receptor alpha mAb, a follow up phase IIb clinical trial showed no significant change in ISS7 or UAS7 compared to placebo. [78,79]Mepolizumab, an anti-IL-5 mAb, has shown effectiveness in case reports of severe-eosinophilic asthma with concomitant CSU, but does not have primary indication for the management of CSU.[80]

***IL-17:***

Secukinumab is an anti-IL-17A antibody currently approved for the treatment of psoriasis. Atwa et al reported that CSU patients had significantly higher levels of IL-17, IL-23, and TNF-α compared to healthy controls.[81] Thus, Sabag et al administered once weekly 150mg subcutaneous secukinumab in 8 patients with severe CSU, who were refractory to omalizumab and cyclosporine.[82] They found that it was highly effective in these patients with a 55% reduction in UAS7 from baseline after 30 days of treatment, and this increased to 82% reduction by 90 days. During the study period, three patients noted mild injection site irritations, but no other serious adverse events were reported.[82] Currently, there are no active phase 3 trials investigating this treatment for CSU.

**Novel Mast Cell Targeted Therapies:**

***BTK inhibitors:***

Bruton tyrosine kinase (BTK) is a protein tyrosine kinase shown to play a role in the immune mediated pathogenesis of CSU through IgE and IgG mediated signaling in mast cells and basophils, as well as autoreactive B cells.[22] Given this mechanism of action, there has been optimism that these agents may prove efficacious in the management of type I and type IIb CSU. Fenebrutinib, an oral selective BTK inhibitor, completed phase 2 double blind placebo control trial for H1-antihistamine refractory CSU[83]. Fenebrutinib demonstrated statistically significant efficacy in subjects with and without type IIb autoimmunity. However, transient asymptomatic liver elevations were observed leading to questions about future development in CSU.

Remibrutinib, an oral BTK inhibitor, completed phase 2b and Phase 3 clinical trials and was found to be effective in reducing urticaria disease activity within the first two weeks of therapy and subjects had a sustained response, along with demonstrating a favorable safety

profile.[84-86] Remibrutinib demonstrated a fast onset of action as early as week one and was significantly more effective at week 24 in improving UAS7 scores compared to placebo. Patients receiving placebo who were switched to remibrutinib, also demonstrated significant improvement in UAS7 scores sustained to week 52. At week 52, approximately 50% of patients showed complete response to treatment with remibrutinib (UAS7 = 0).[85,86] Importantly, remibrutinib demonstrated greater efficacy vs placebo, independent of prior exposure to anti-IgE biologics.[87] This therapy is currently being considered for approval by the FDA.

Rilzabrutinib, an oral reversible covalent BTK inhibitor, was also assessed in a double-blind RCT in adult CSU patients refractory to H1-antihistamines and demonstrated statistically significant reduction in UAS7 and itch severity scores at 12 weeks.[ 88] Of interest was Rilzabrutinib's rapid onset of action and reduction in pruritus scores from first week of treatment.[88]

BTK inhibitors have been investigated for the potential risk of immunomodulatory effects on mean immunoglobulin levels or risk of infection, however, elevated rates of infection have not been observed in clinical trials. [84,85]

***c-KIT:***

Another pathway of therapeutic interest involves targeting the KIT/SCF pathway in mast cells.[89-92] KIT is the receptor for the cytokine stem cell factor (SCF), which is the critical growth factor of mast cells.[90-92] The gene that encodes the receptor KIT is the proto-oncogene c-KIT.[90-92] Barzolvolimab (CDX-0159) is an IgG1 monoclonal antibody that targets c-KIT, a tyrosine kinase receptor, inhibiting the binding to its ligand stem cell factor (SCF). [94] A single center, open-label phase 1b study looked at the efficacy of a single dose of barzolvolimab in 20 patients with cold urticaria and symptomatic dermographism.[93] Nineteen of 20 patients

achieved complete response during the 12-week follow-up period. UCT scores were ≥ 12, demonstrating well-controlled disease, by week 8 in all 20 patients. Dermatology life quality index scores (DLQI) scores improved in all patients by week 4. While the treatment was well tolerated, all patients experienced adverse effects, which were mostly mild and commonly included reversible neutropenia, lightened hair color, hypopigmentation of skin, infusion reactions, and taste changes.[93] A Phase 2 study confirmed efficacy and safety.[94] Two Phase 3 studies are currently recruiting patients at time of publication (NCT06445023, NCT06455202).

Another immunoglobulin G1 anti-KIT antibody, Briquilimab, is under clinical investigation in the BEACON phase 1b/2a dose escalation study in adult patients with CSU.[95]

***MRGPRX2:***

Mas-related G protein-coupled receptor X2 (MRGPRX2, also known as MRGX2) has garnered therapeutic interest given its demonstration of IgE-independent activation of mast cells, basophils and eosinophils.[96] MRGPRX2 has been shown to be a receptor for neuropeptides, antimicrobial peptides, proteases and variety of drugs including opiates, fluoroquinolones, vancomycin, bradykinin receptor antagonists and neuromuscular blocking agents. [97] The number of MRGPRX2-positive skin mast cells and the percentage of MRGPRX2-positive mast cells in all mast cells evaluated in patients with CSU were significantly greater than those in healthy control subjects. s.[98] Clinical application of these compounds are promising. However. a recent Phase 2 study of MRGPRX2 antagonist INCB000262 has been paused following observation of certain in vivo preclinical toxicology findings.[99]

Evoimmune is investigating a MRGPRX2 compound recently completed a Phase2a study in CIndU (cold induced urticaria and symptomatic dermatographism; NCT06603220) and a

Phase 2b study (NCT06873516) investigating its efficacy in moderate to severe CSU patients not responsive to H1-antihistamines is underway.

***Siglec-6/ Siglec-8:***

Sialic acid binding immunoglobulin-like lectins (Siglecs) are a family of inhibitory regulatory receptors that have been shown to be expressed on mast cell and eosinophils.[100] Pre-clinical research utilizing murine mast cells suggested a potential role for Siglec-6 and Siglec-8 inhibition of stem cell factor mediated mast cell activation.[101] However, clinical trials have been underwhelming. An open-label phase 2a study evaluated Lirentelimab, an IgG1 monoclonal antibody inhibiting Siglec-8 in CSU and CIndU (cholinergic and dermographic urticaria). The study found that disease control and severity improved, as seen by the changes in the UCT, UAS7, and CholUAS7 scores.[102] Unfortunately, the phase 2b clinical trial did not meet its primary endpoint (change in UAS7 at week 12), so subsequent investigations are currently on hold.[103] AK006, a selective anti-Siglec-6, did not demonstrate therapeutic activity in its phase 1 clinical trial.[103]

***JAK Inhibitors:***

Given the ability for selective JAK1 inhibitors to modulate IL-4, IL-13, IL-22, IL-31 and TSLP and improve clinical outcomes in patients with atopic dermatitis, there has been growing therapeutic interest for use in refractory CSU.[104,105] Preliminary evidence from ruxolitinib and tofacitinib are encouraging.[106,107]. A recent retrospective analysis showed abrocitinib (Cibinqo™) significantly improved clinical outcomes in adult CSU patients with antihistamine refractory urticaria with inadequate response to omalizumab. [108] One study (NCT06396026) investigating TLL-018, a TYK2/JAK1 inhibitor, in CSU is currently recruiting at the time of this study **(Table 1).**

## Conclusions

In summary, CSU is a prevalent condition that has a significant impact on patient's QOL. Although advancements in understanding the pathogenesis of CSU have been made, there are still gaps in knowledge. Current guidelines provide evidence-based recommendations for assessment and management of this condition. Novel therapies are currently being developed to improve control of CSU in patients not responsive to omalizumab, or who do not respond or are not able to tolerate cyclosporin due to adverse side effects. Recently, dupilumab was approved for patients 12 years of age and older in the United States for CSU. Remibrutinib for treatment of CSU has been submitted to the FDA and is awaiting a decision. The role of biomarkers to predict responders and non-responders to $H_1$-antihistamines and omalizumab have been identified, but whether these tests predict response to future therapies is still unclear. However, it is important to diagnose CSU with or without CIndU promptly and initiate therapy using current guideline recommended algorithms to reduce the patient's disease burden.

List of Figure Captions

**Figure 1.** Type I and Type IIb CSU Endotypes.[24]

**Figure 2**. Current and Potential Future Mast Cell Targets for CSU. [30]

**Figure 3.** 2022 International Updated Guidelines.[37]

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**Table 1. Active, Completed, And Terminated Biologic Trials For Chronic Spontaneous Urticaria (CSU)**

| NCT Number | Study Title | Study Status | Sponsor |
|---|---|---|---|
| NCT06873516 | Phase 2b Study of EVO756 (MRGPRX2 receptor antagonist) in Adults with Moderate to Severe Chronic Spontaneous Urticaria (CSU) | NOT_YET_ RECRUITING | Evommune, Inc. |
| NCT06931405 | Study of BLU-808 in Chronic Inducible Urticaria (CIndU) and Chronic Spontaneous Urticaria (CSU) | NOT_YET_ RECRUITING | Blueprint Medicines Corporation |
| NCT06864507 | A Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of HS-10561 (BTKi) Capsule in Healthy Chinese Adults and Patients With Chronic Spontaneous Urticaria. | NOT_YET_ RECRUITING | Jiangsu Hansoh Pharmaceutical Co., Ltd. |
| NCT06868212 | A Study to Evaluate Efficacy of Remibrutinib Compared to Dupilumab at Early Timepoints in Adults With Chronic Spontaneous Urticaria Inadequately Controlled by Second Generation H1-antihistamines | NOT_YET_ RECRUITING | Novartis Pharmaceuticals |
| NCT06250400 | Efficacy and Safety of Histamine Human Immunoglobulin in the Treatment of Chronic Spontaneous Urticaria (CSU) | NOT_YET_ RECRUITING | Hangzhou Grand Biologic Pharmaceutical, Inc. |
| NCT06445023 | A Phase 3 Study of Barzolvolimab (wild type ckit inhibitor) in Participants With Chronic Spontaneous Urticaria | RECRUITING | Celldex Therapeutics |
| NCT06865651 | Study of Remibrutinib (LOU064) Efficacy and Safety and Exploration of Its Mechanism of Action in Participants With Chronic Urticaria | NOT_YET_ RECRUITING | Novartis Pharmaceuticals |
| NCT05513001 | An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib | ACTIVE_NOT_ RECRUITING | Novartis Pharmaceuticals |
| NCT05936567 | Study Evaluating the Efficacy and Safety of Povorcitinib in Adults With Chronic Spontaneous Urticaria | ACTIVE_NOT_ RECRUITING | Incyte Corporation |
| NCT06604949 | A Study of Single Dose of LP-003 (omalizumab biosimilar) in Healthy Adult Subjects | NOT_YET_ RECRUITING | Longbio Pharma |
| NCT06294288 | A Study of Single and Multiple Doses of LP-003 (omalizumab biosimilar) in Healthy Adult Participants | ACTIVE_NOT_ RECRUITING | Longbio Pharma |
| NCT04175704 | Evaluating the Safety and Tolerability and Determining the PK and PD of Single Dose UB-221 (Ligelizumab) in Chronic Spontaneous Urticaria | NOT_YET_ RECRUITING | United BioPharma |
| NCT04404023 | Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Immunogenicity of UB-221 in Healthy Volunteers | NOT_YET_ RECRUITING | UBP Greater China (Shanghai) Co., Ltd |
| NCT05677451 | 24 Weeks Double-blind Randomized Placebo-controlled Trial to Evaluate Efficacy, PK, Safety of LOU064 (Remibrutinib; BTKi) in Adolescents (12 - <18) With CSU and Inadequate Response to H1-antihistamine Followed by Optional 3 Years Open-label Extension and an Optional 3 Years Safety Long-term Treatment-free Follow-up | RECRUITING | Novartis Pharmaceuticals |

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| NCT06042478 | Phase 3b Study to Assess the Efficacy, Safety, and Tolerability of Remibrutinib in Comparison to Placebo, With Omalizumab as Active Control, in Adult CSU Patients, Followed by an Open-label 52-week Optional Extension. | RECRUITING | Novartis Pharmaceuticals |
| NCT06053801 | A Real-world Study to Assess Safety and Effectiveness of XolairÂ® in Pediatric Chronic Spontaneous Urticaria in China | RECRUITING | Novartis Pharmaceuticals |
| NCT05170724 | Global Managed Access Program Cohort for Remibrutinib (BTKi) in Adult Patients With Chronic Spontaneous Urticaria | AVAILABLE | Novartis Pharmaceuticals |
| NCT06455202 | A Phase 3 Study of Barzolvolimab in Participants With Chronic Spontaneous Urticaria (CSU) | RECRUITING | Celldex Therapeutics |
| NCT06365879 | To Compare Efficacy and Safety of CMAB007 (omalizumab biosimilar) and XolairÂ® in Patients With Chronic Spontaneous Urticaria | RECRUITING | Taizhou Mabtech Pharmaceutical Co.,Ltd |
| NCT06509334 | Trial of JYB1904 (long active anti-IgE monoclonal antibody) in Chronic Spontaneous Urticaria. | RECRUITING | Jemincare |
| NCT06162728 | Dose Escalation Trial of Safety, Pharmacokinetic/Pharmacodynamic and Preliminary Clinical Activity of Briquilimab (wild type ckit inhibitor) in Adult Patients with Chronic Spontaneous Urticaria (CSU) | RECRUITING | Jasper Therapeutics, Inc. |
| NCT06924762 | Interleukin-2 for Refractory Chronic Spontaneous Urticaria | RECRUITING | Second Xiangya Hospital of Central South University |
| NCT06555328 | Evaluate Safety and Pharmacokinetics of INF904 in Subjects With Moderate to Severe Chronic Spontaneous Urticaria or Hidradenitis Suppurativa | RECRUITING | InflaRx GmbH |
| NCT06295302 | A Study to Explore the Efficacy and Safety of HWH486 (BTKi) in Adults With Chronic Spontaneous Urticaria | RECRUITING | Hubei Biological Medicine Industrial Technology Institute Co., Ltd. |
| NCT06795373 | Ritlecitinib (PF-06651600) in Participants With Chronic Spontaneous Urticaria | RECRUITING | Ahuva D Cices |
| NCT06228560 | Efficacy and Safety of LP-003 in Patients With CSU Who Remain Symptomatic Despite Antihistamine (H1) Treatment | RECRUITING | Longbio Pharma |
| NCT06396026 | A Study of Efficacy and Safety of TLL-018 in CSU Participants | RECRUITING | Hangzhou Highlightll Pharmaceutical Co., Ltd |
| NCT04426890 | To Compare Efficacy and Safety of CT-P39 (Omalizumab biosimilar) and EU-approved Xolair in Patients With Chronic Spontaneous Urticaria | COMPLETED | Celltrion |
| NCT05373355 | Safety and Efficacy of TLL018 (TYK2/JAK1 inhibitor), in Patients With Chronic Spontaneous Urticaria. | COMPLETED | Hangzhou Highlightll Pharmaceutical Co., Ltd |
| NCT05335499 | A Phase 2a Study of TAS5315 in Patients With Chronic Spontaneous Urticaria | COMPLETED | Taiho Pharmaceutical Co., Ltd. |
| NCT05368285 | A Phase 2 Study of CDX-0159 in Patients With Chronic Spontaneous Urticaria | COMPLETED | Celldex Therapeutics |
| NCT02372604 | Efficacy of Levocetirizine Fourfold Dosage in Chronic Spontaneous Urticaria | COMPLETED | Hospices Civils de Lyon |
| NCT04833855 | Study to Evaluate Tezepelumab in Adults With Chronic Spontaneous Urticaria | COMPLETED | Amgen |

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| NCT03437278 | Study to Investigate the Efficacy and Safety of QGE031 in Adolescent Patients With Chronic Spontaneous Urticaria (CSU) | COMPLETED | Novartis Pharmaceuticals |
| NCT03328897 | Study of Efficacy and Safety of XolairÂ® (Omalizumab) in Chinese Patients With Chronic Spontaneous Urticaria | COMPLETED | Novartis Pharmaceuticals |
| NCT03494881 | Mepolizumab for the Treatment of Chronic Spontaneous Urticaria | COMPLETED | Mayo Clinic |
| NCT04538794 | A Study of CDX-0159 in Patients With Chronic Spontaneous Urticaria | COMPLETED | Celldex Therapeutics |
| NCT02550106 | Omalizumab in Chronic Spontaneous Urticaria Patients Non Responding to Initial Standard antihistaminE Treatment | COMPLETED | Novartis Pharmaceuticals |
| NCT05795153 | A Multicenter, Open-label Phase 3 Study: Ambulatory Blood Pressure Monitoring in Adult Patients With Chronic Spontaneous Urticaria Inadequately Controlled by H1-antihistamines Treated With Remibrutinib up to 12 Weeks. | COMPLETED | Novartis Pharmaceuticals |
| NCT05526521 | A Study to Investigate the Pharmacokinetics and Safety of Dupilumab in Participants 2 Years to <12 Years of Age With Uncontrolled Chronic Spontaneous Urticaria (CSU) (LIBERTY-CSU CUPIDKids) | COMPLETED | Sanofi |
| NCT05107115 | Rilzabrutinib for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine | COMPLETED | Sanofi |
| NCT02649218 | A Safety Extension Study to Evaluate the Long-term Safety of QGE031 in Chronic Spontaneous Urticaria (CSU) Patients | COMPLETED | Novartis Pharmaceuticals |
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| NCT05030311 | A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1 Antihistamines | COMPLETED | Novartis Pharmaceuticals |
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| NCT02161562 | OPTIMA: Efficacy of Optimized Re-treatment and Step-up Therapy With Omalizumab in Chronic Spontaneous Urticaria (CSU) Patients | COMPLETED | Novartis Pharmaceuticals |
| NCT05048342 | A Safety and Efficacy Study of Remibrutinib in the Treatment of CSU in Japanese Adults Inadequately Controlled by H1-antihistamines | COMPLETED | Novartis Pharmaceuticals |
| NCT05032157 | A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-antihistamines | COMPLETED | Novartis Pharmaceuticals |
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| NCT03580369 | A Phase III Study of Safety and Efficacy of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-antihistamines | COMPLETED | Novartis Pharmaceuticals |
| NCT03580356 | A Phase III Study of and Efficacy of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-antihistamines. | COMPLETED | Novartis Pharmaceuticals |
| NCT04180488 | Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine and Who Are naÃ¯ve to, Intolerant of, or Incomplete Responders to Omalizumab (LIBERTY-CSU CUPID) | COMPLETED | Sanofi |

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| NCT03907878 | A Safety and Efficacy Study of Ligelizumab in the Treatment of CSU in Japanese Patients Inadequately Controlled With H1-Antihistamines | COMPLETED | Novartis Pharmaceuticals |
| NCT03926611 | This Was a Dose-finding Study to Evaluate Efficacy and Safety of LOU064 in Patients With CSU Inadequately Controlled by H1-antihistamines | COMPLETED | Novartis Pharmaceuticals |
| NCT02477332 | Dose-finding Study of QGE031 as add-on Therapy to Evaluate Efficacy and Safety in Patients With CSU | COMPLETED | Novartis Pharmaceuticals |
| NCT04109313 | An Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of LOU064 in Subjects With CSU | COMPLETED | Novartis Pharmaceuticals |
| NCT01803763 | Prospective Double-blind Placebo-controlled Study of the Effect of Xolair (Omalizumab) in Chronic Urticaria Patients | COMPLETED | Insel Gruppe AG, University Hospital Bern |
| NCT01723072 | Impact of Omalizumab on Quality of Life Measures and Angioedema Occurrence in Patients With CSU Refractory to Therapy | COMPLETED | Novartis Pharmaceuticals |
| NCT02329223 | Study of Efficacy and Safety of Omalizumab in Refractory Chronic Spontaneous Urticaria Patients | COMPLETED | Novartis Pharmaceuticals |
| NCT03749135 | Dupilumab in Chronic Spontaneous Urticaria | COMPLETED | Charite University, Berlin, Germany |
| NCT03137069 | A Study of GDC-0853 in Participants With Refractory Chronic Spontaneous Urticaria (CSU). | COMPLETED | Genentech, Inc. |
| NCT04976192 | Study to Compare Efficacy and Safety of TEV-45779 With XOLAIR (Omalizumab) in Adults With Chronic Idiopathic Urticaria | COMPLETED | Teva Pharmaceuticals USA |
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| NCT05960708 | A Single Dose, Phase 1 Study of YH35324 in Patients with Various Allergic Diseases | COMPLETED | Yuhan Corporation |
| NCT03632291 | Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of UB-221 as an Add-on Therapy in CSU Patients | COMPLETED | United BioPharma |
| NCT01287117 | A Study of the Efficacy and Safety of Omalizumab (Xolair) in Patients With Chronic Idiopathic Urticaria (CIU)/Chronic Spontaneous Urticaria (CSU) Who Remain Symptomatic Despite Antihistamine (H1) Treatment | COMPLETED | Genentech, Inc. |
| NCT01987947 | A Study of Quilizumab Versus Placebo in Patients With Refractory Chronic Spontaneous Urticaria | COMPLETED | Genentech, Inc. |
| NCT01292473 | A Study to Evaluate the Efficacy, Response Duration and Safety of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU)/Chronic Spontaneous Urticaria (CSU) Who Remain Symptomatic Despite Antihistamine Treatment (H1) | COMPLETED | Genentech, Inc. |
| NCT01713725 | Efficacy and Safety Study of Omalizumab (XolairÂ®) to Treat Chronic Urticaria | COMPLETED | Clinica Universidad de Navarra, Universidad de Navarra |
| NCT00866788 | A Study of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic With Antihistamine Treatment (H1) | COMPLETED | Genentech, Inc. |

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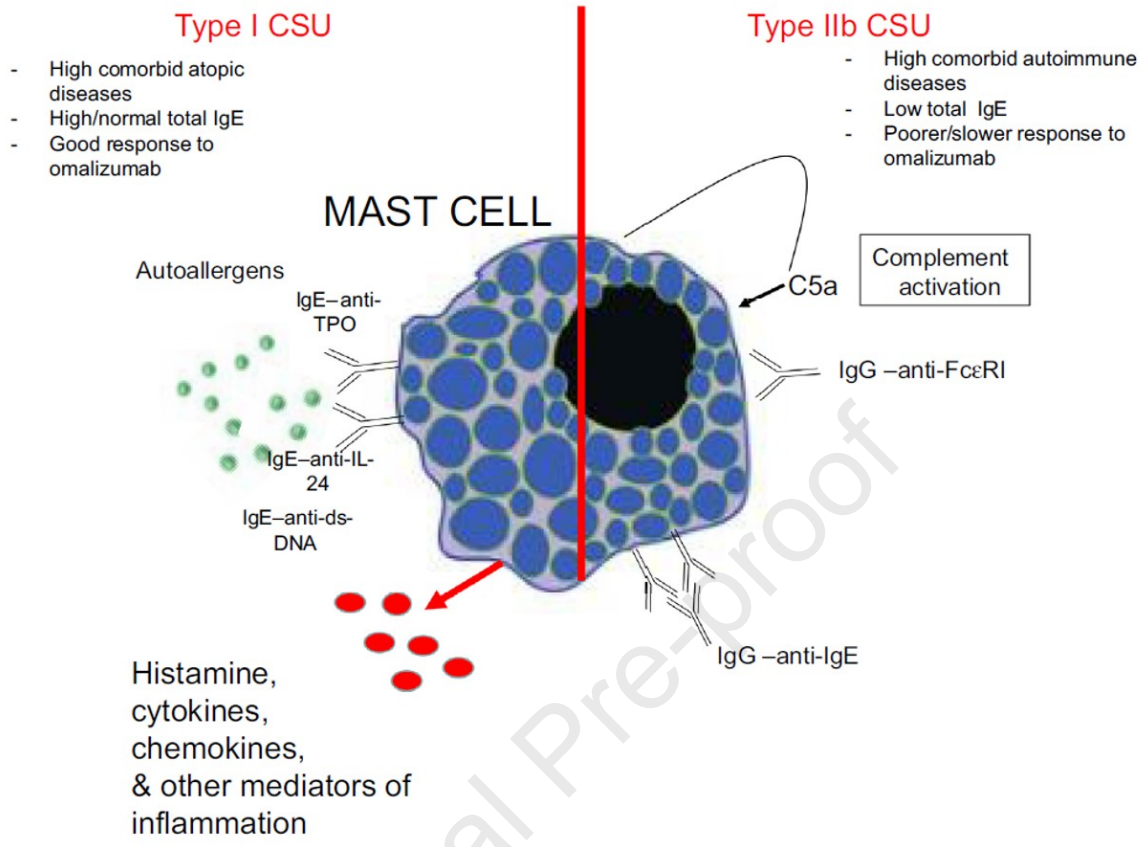
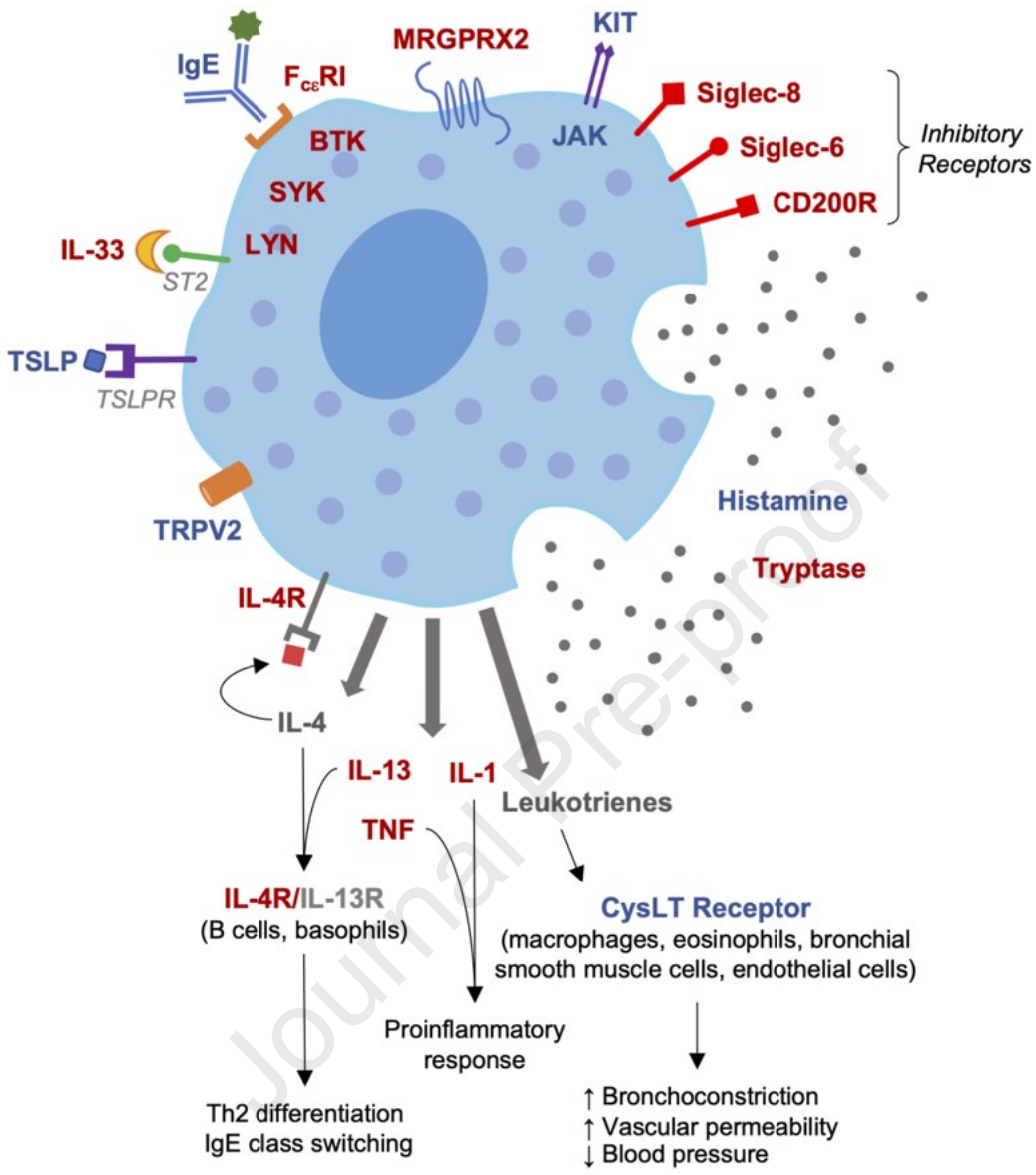
| NCT01264939 | A Safety Study of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists | COMPLETED | Genentech, Inc. |
| NCT03183024 | Treatment of Chronic Urticarial Unresponsive to H1-antihistamines With an Anti-IL5Ralpha Monoclonal Antibody | COMPLETED | Jonathan A. Bernstein, MD |
| NCT02424799 | Study to Investigate Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of GSK2646264 | COMPLETED | GlaxoSmithKline |
| NCT06077773 | Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP262 in Subjects With Chronic Spontaneous Urticaria | TERMINATED | Escient Pharmaceuticals, Inc |
| NCT06072157 | Study to Assess the Safety, Tolerability, Pharmacokinetics and Immunogenicity of AK006 in Healthy Subjects and Subjects With Chronic Spontaneous Urticaria | TERMINATED | Allakos Inc. |
| NCT04827589 | Study to Evaluate the Efficacy, Safety, and Tolerability of Tirabrutinib (BTK1) in Participants With Antihistamine-Resistant Chronic Spontaneous Urticaria | WITHDRAWN | Gilead Sciences |
| NCT05129423 | A Study of MTPS9579A (monoclonal antibody that selectively inhibits tryptase activity by dissociating active tetramers into inactive monomers) in Participants With Refractory Chronic Spontaneous Urticaria | WITHDRAWN | Genentech, Inc. |
| NCT01030120 | Etanercept for the Treatment of Chronic Urticaria | WITHDRAWN | University of Utah |
| NCT01635127 | Efficacy Study of Canakinumab to Treat Urticaria | UNKNOWN | University of Zurich |
| NCT04944602 | Study to Evaluate the Therapeutic Equivalence of SYN008 Versus Xolair® in the Treatment of Patients With Refractory Chronic Spontaneous Urticaria | UNKNOWN | CSPC Baike (Shandong) Biopharmaceutical Co., Ltd. |

**Table 2. Active, Completed, And Terminated Biologic Trials For Chronic Inducible Urticaria (CIndU)**

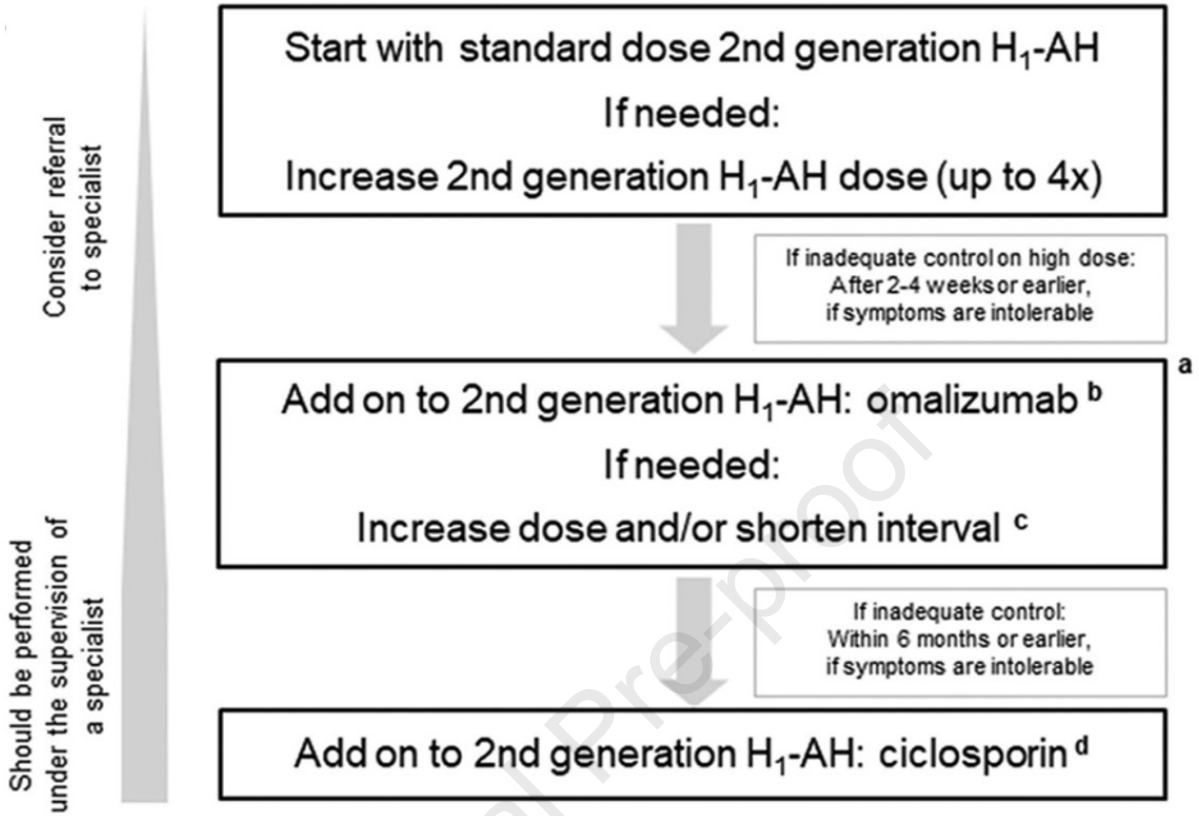
| NCT Number | Study Title | Study Status | Sponsor |
|---|---|---|---|
| NCT06353971 | A Dose Escalation Trial of Safety, Pharmacokinetic/Pharmacodynamic and Preliminary Clinical Activity of Briquilimab in Adult Patients With CIndUWho Remain Symptomatic Despite Treatment With H1- Antihistamines | RECRUITING | Jasper Therapeutics, Inc. |
| NCT05976243 | A Study to Investigate Efficacy, Safety, and Tolerability of Remibrutinib Compared With Placebo in Adults With CINDU Inadequately Controlled by H1-antihistamines | RECRUITING | Novartis Pharmaceuticals |
| NCT05405660 | A Study of CDX-0159 in Patients With CIndU | ACTIVE_NOT_ RECRUITING | Celldex Therapeutics |
| NCT06931405 | Study of BLU-808 in CIndU and CSU | NOT_YET_ RECRUITING | Blueprint Medicines Corporation |
| NCT06603220 | A Study Evaluating the Safety, Tolerability, and Efficacy of EVO756 in Adults With CIndU | ACTIVE_NOT_ RECRUITING | Evommune, Inc. |
| NCT06865651 | Study of Remibrutinib (LOU064) Efficacy and Safety and Exploration of Its Mechanism of Action in Participants With Chronic Urticaria | NOT_YET_ RECRUITING | Novartis Pharmaceuticals |
| NCT04513548 | Study of Mechanism of Action of Ligelizumab (QGE031) in Patients With Chronic Urticaria | TERMINATED | Novartis Pharmaceuticals |
| NCT05024058 | Study of Efficacy and Safety of Ligelizumab in Adolescents and Adults With CIndU Who Remain Symptomatic Despite Treatment With H1-Antihistamines | TERMINATED | Novartis Pharmaceuticals |
| NCT06050928 | Phase 1b, Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects With CIndU | COMPLETED | Escient Pharmaceuticals, Inc |
| NCT04681729 | Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic Despite the Use of H1-antihistamine (LIBERTY-CINDU CUrIADS) | COMPLETED | Sanofi |
| NCT05960708 | A Single Dose, Phase 1 Study of YH35324 in Patients with Various Allergic Diseases | COMPLETED | Yuhan Corporation |
| NCT01360658 | Intravenous Immunoglobulins in Severe and Refractory Solar Urticaria | COMPLETED | Centre Hospitalier Universitaire de Besancon |
| NCT02262130 | Omalizumab in Severe and Refractory Solar Urticaria | COMPLETED | Centre Hospitalier Universitaire de Besancon |
| NCT00214851 | The Use of Kineret (Anakinra) in the Treatment of Familial Cold Urticaria | COMPLETED | Nova Scotia Health Authority |






**Blue = Targets of approved therapies**
**Red = Targets of investigational therapies**

NOTE: Intracellular signaling molecules are expressed in many cell types, not limited to mast cells




**a** Second line and third line treatment apply only for CU
**b** 300mg every 4 weeks
**c** Up to 600mg every 2 weeks
**d** Up to 5mg/kg body weight