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MEDIA & INVESTOR RELEASE

Novartis data show potential of remibrutinib as an oral treatment for chronic spontaneous urticaria providing significant symptom improvement as early as Week 2

- *In pivotal Phase III trials, remibrutinib – a highly selective, oral Bruton's tyrosine kinase inhibitor – demonstrated clinically meaningful and statistically significant reduction in urticaria activity vs placebo*[1]

- *Treatment with remibrutinib led to significant improvement in symptom control, as early as Week 2 and sustained up to Week 12*[1]

- *Remibrutinib was well-tolerated and demonstrated a favorable safety profile with rates of overall adverse events comparable to placebo and balanced liver function tests across both studies*[1]

- *REMIX-1 and REMIX-2 studies are ongoing, with final (52-week) readout and regulatory submissions in 2024*

Basel, November 9, 2023 — Novartis today announced new positive data from the Phase III REMIX-1 and REMIX-2 studies investigating remibrutinib – a highly selective, oral Bruton's tyrosine kinase (BTK) inhibitor – in people with chronic spontaneous urticaria (CSU) whose symptoms are inadequately controlled by H1-antihistamines[1]. In the studies, remibrutinib met all primary and secondary endpoints at Week 12[1]. Remibrutinib demonstrated superiority in change from baseline vs placebo in weekly urticaria activity (UAS7), itch (ISS7) and hives (HSS7) at Week 12[1]. Significantly more patients achieved well-controlled disease (UAS7≤6) with remibrutinib vs placebo, as early as Week 2 which was sustained at Week 12, and about one third of patients achieved complete absence of itch and hives at Week 12[1]. Data are being presented at the 2023 American College of Allergy, Asthma and Immunology Scientific Meeting in Anaheim, California, November 9–13.

"These findings could be significant for the millions of people who suffer from CSU and are still symptomatic," said Marcus Maurer, M.D., Professor of Dermatology and Allergy, Executive Director of the Institute of Allergology at Charité – Universitätsmedizin Berlin and Co-Director of Allergy and Immunology at the Fraunhofer Institute for Translational Medicine and Pharmacology. "Living with CSU can be very distressing, often impacting many aspects of people's lives such as sleep and ability to work. Having another option that could potentially provide effective relief as early as 2 weeks after trying antihistamines alone could be transformative for these patients."

Mean change from baseline (CFB) in UAS7, ISS7 and HSS7 at Week 12 in REMIX-1 and REMIX-2[1]

	REMIX-1		REMIX-2	
LS mean ±SE	Remibrutinib (n=309)	Placebo (n=153)	Remibrutinib (n=297)	Placebo (n=153)
CFB-UAS7	–20.1 ±0.7	–13.8 ±1.0	–19.6 ±0.7	–11.7 ±0.9
CFB-ISS7	–9.6 ±0.3	–6.9 ±0.5	–9.0 ±0.3	–5.7 ±0.5
CFB-HSS7	–10.5 ±0.4	–6.9 ±0.5	–10.5 ±0.4	–6.0 ±0.5

LS, least squares; SE, standard error.

In pooled safety analyses of the REMIX studies, remibrutinib demonstrated a well-tolerated and favorable safety profile, with overall adverse event rates that were comparable to placebo (64.0% in remibrutinib vs 64.7% in placebo), including infections (32.8% in remibrutinib vs 34.0% in placebo) and liver function test abnormalities. Liver transaminase elevations were balanced across both treatment groups (remibrutinib and placebo), asymptomatic, transient and reversible[1]. None of the serious adverse events were considered related to study medication by investigators.

“Patients with CSU have limited treatment options and many patients do not respond to antihistamines even at higher than approved doses, leaving them with uncontrolled symptoms and potential side effects such as drowsiness,” said Angelika Jahreis, Global Head, Development, Immunology, Novartis. “We are committed to developing new therapies for patients with immuno-dermatologic disorders and are excited about the prospect to provide a potential new option for patients with CSU who suffer from relentless itch and a life filled with limitations. These data show that remibrutinib, an oral BTKi, provided significant symptom improvement as early as Week 2 and sustained up to Week 12.”

Antihistamines are recommended to treat CSU but are not always effective[2]. International guidelines recommend increasing the approved dose up to four-fold, but people can still have uncontrolled symptoms, even at high doses[3]. While injectable biologic therapies are an effective option for those whose CSU is uncontrolled by antihistamines, less than 20% of eligible patients worldwide are treated with them[4].

CSU is the medical term for chronic hives that last for 6 weeks or longer, where the underlying cause is internal rather than exposure to any allergen or external trigger[5,6]. In CSU, BTK is believed to play a role in the signaling pathway that leads to the release of histamine and debilitating symptoms[7]. Remibrutinib blocks BTK and prevents the release of histamine that causes itchy hives (wheals) and/or deep tissue swelling (angioedema)[6,8].

Patients currently enrolled in REMIX-1 and REMIX-2 will continue to receive treatment up to Week 52 and will have the opportunity to continue in a long-term extension trial. Novartis intends to submit remibrutinib to global health authorities starting in 2024.

About remibrutinib

Remibrutinib is an investigational highly selective, covalent, oral BTK inhibitor that blocks the BTK cascade and prevents the release of histamine that causes itchy hives (wheals) and swelling[6-8]. In Phase III studies, treatment with remibrutinib led to significant improvement in symptom control, as early as Week 2 and sustained up to Week 12[1]. Significantly more patients achieved well-controlled disease (UAS7≤6) with remibrutinib vs placebo, as early as Week 2 which was sustained at Week 12, and about one third of patients achieved complete absence of itch and hives at Week 12[1]. Remibrutinib has been shown to be well-tolerated with a favorable safety profile, with balanced liver function test results across studies[1]. Most

commonly observed (occurring in ≥3% of patients during the 24-Week double-blind period) adverse events in the Phase III REMIX studies were respiratory tract infections (COVID-19 and nasopharyngitis, both comparable to placebo)[1]. In addition to CSU, remibrutinib is being investigated in other immune-mediated conditions, such as multiple sclerosis, hidradenitis suppurativa, food allergy and Sjögren's disease[9-13]. If approved, remibrutinib has the potential to become an effective oral option to complement Xolair® (omalizumab), the first and only injectable biologic indicated for CSU[14]. In the US, Novartis Pharmaceuticals Corporation and Genentech, a member of the Roche Group, work together to develop and co-promote Xolair.

About REMIX-1 and REMIX-2

REMIX-1 (NCT05030311) and REMIX-2 (NCT05032157) are two identically designed global, multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase III studies, with REMIX-1 consisting of 470 participants and REMIX-2 consisting of 455 participants[15,16]. Both studies are designed to establish the efficacy, safety, and tolerability of twice-daily remibrutinib 25 mg treatment in adult participants with CSU that is inadequately controlled by second generation H1-antihistamines compared with placebo[15,16]. The primary outcome measures include absolute change from baseline in UAS7, absolute change in ISS7 and HSS7 at Week 12[15,16]. All participants were on a stable, locally label-approved dose of a second-generation H1-antihistamine throughout the entire study. Patients currently enrolled in REMIX-1 and REMIX-2 will continue to receive treatment up to Week 52 and will have the opportunity to continue in a long-term extension trial[15,16].

About CSU

CSU affects approximately 40 million people worldwide[5,17]. It is characterized by the sudden appearance of itchy hives (wheals) and/or deep tissue swelling (angioedema, which can occur on the face, throat, hands, and feet) for more than 6 weeks[6,18]. CSU affects all ages but most frequently between the ages of 20–40, with women affected nearly twice as often as men[5]. CSU causes significant emotional distress, with the majority of patients suffering from sleep deprivation, and high rates of mental disorders, such as anxiety or depression, as well as impact on their work productivity[5]. There are currently limited effective treatment options for CSU, with many patients not achieving full control from the first-line treatment, antihistamines[2].

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disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis is a focused innovative medicines company. Every day, we work to reimagine medicine to improve and extend people's lives so that patients, healthcare professionals and societies are empowered in the face of serious disease. Our medicines reach more than 250 million people worldwide.

Reimagine medicine with us: Visit us at https://www.novartis.com and connect with us on LinkedIn, Facebook, X/Twitter and Instagram.

References

1. Sarbjit S, Giménez-Arnau A, Hide M, et al. Fast Symptom Improvement and Favorable Safety Profile With Remibrutinib in Chronic Spontaneous Urticaria: REMIX-1/-2 Studies. Presented as a late-breaking abstract at ACAAI 2023.
2. Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Ontoso E, et al. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol.* 2016;175:1153–1165.
3. Weller K, Church M, Kalogeromitros D, et al. Chronic spontaneous urticaria: how to assess quality of life in patients receiving treatment. Available from: https://jamanetwork.com/journals/jamadermatology/fullarticle/1105319 [Last accessed: November 2023].
4. Novartis Data on File.
5. Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA^{2}LEN task force report. *Allergy.* 2011;66:317–330.
6. Powell RJ, Leech SC, Till S, *et al.* BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy.* 2015;45:547–565.
7. Maurer M, Berger W, Gimenez-Arnau A, et al. Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria. *J Allergy Clin Immunol.* 2022;150:1498–1506.
8. Angst D, Gessier F, Janser P, et al. Discovery of LOU064 (Remibrutinib), a Potent and Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase. *J Med Chem.* 2020;63:5102–5118.
9. ClinicalTrials.gov. NCT05156281. Efficacy and Safety of Remibrutinib Compared to Teriflunomide in Participants With Relapsing Multiple Sclerosis (RMS). Available from: https://clinicaltrials.gov/study/NCT05156281 [Last accessed: November 2023].
10. ClinicalTrials.gov. NCT05147220. Efficacy and Safety of Remibrutinib Compared to Teriflunomide in Participants With Relapsing Multiple Sclerosis. Available from: https://clinicaltrials.gov/study/NCT05147220 [Last accessed: November 2023].
11. ClinicalTrials.gov. NCT03827798. Study of Efficacy and Safety of Investigational Treatments in Patients With Moderate to Severe Hidradenitis Suppurativa. Available from: https://clinicaltrials.gov/study/NCT03827798 [Last accessed: November 2023].
12. ClinicalTrials.gov. NCT05432388. Study of Efficacy, Safety and Tolerability of Remibrutinib in Adult Participants With an Allergy to Peanuts. Available from: https://clinicaltrials.gov/study/NCT05432388 [Last accessed: November 2023].
13. ClinicalTrials.gov. NCT04035668. A Phase 2 Study to Evaluate the Safety and Efficacy of LOU064 in Patients With Moderate to Severe Sjögren's Syndrome (LOUiSSe). Available from: https://clinicaltrials.gov/study/NCT04035668 [Last accessed: November 2023].
14. Genentech USA, Inc. and Novartis Pharmaceuticals Corporation. Xolair Omalizumab. Chronic Spontaneous Urticaria (CSU). Available at: https://www.xolair.com/chronic-spontaneous-urticaria.html [Last accessed: November 2023].
15. Clinical Trials.gov. A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1 Antihistamines (REMIX-1). NCT05030311. Available from: https://clinicaltrials.gov/ct2/show/NCT05030311 [Last accessed: November 2023].
16. Clinical Trials.gov. A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1 Antihistamines (REMIX-2). NCT05032157. Available from: https://clinicaltrials.gov/ct2/show/NCT05032157 [Last accessed: November 2023].
17. The World Bank. Population, total. Available from: https://data.worldbank.org/indicator/SP.POP.TOTL [Last accessed: November 2023].
18. AAAAI. Hives (Urticaria) and Angioedema Overview. Available at: https://www.aaaai.org/tools-for-the-public/conditions-library/allergies/hives-(urticaria)-and-angioedema-overview [Last accessed: November 2023].

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