SCUOLA DERMATOLOGICA
SERGIO CHIMENTI
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Dermatology Update

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Orticaria cronica: un challenge per il dermatologo

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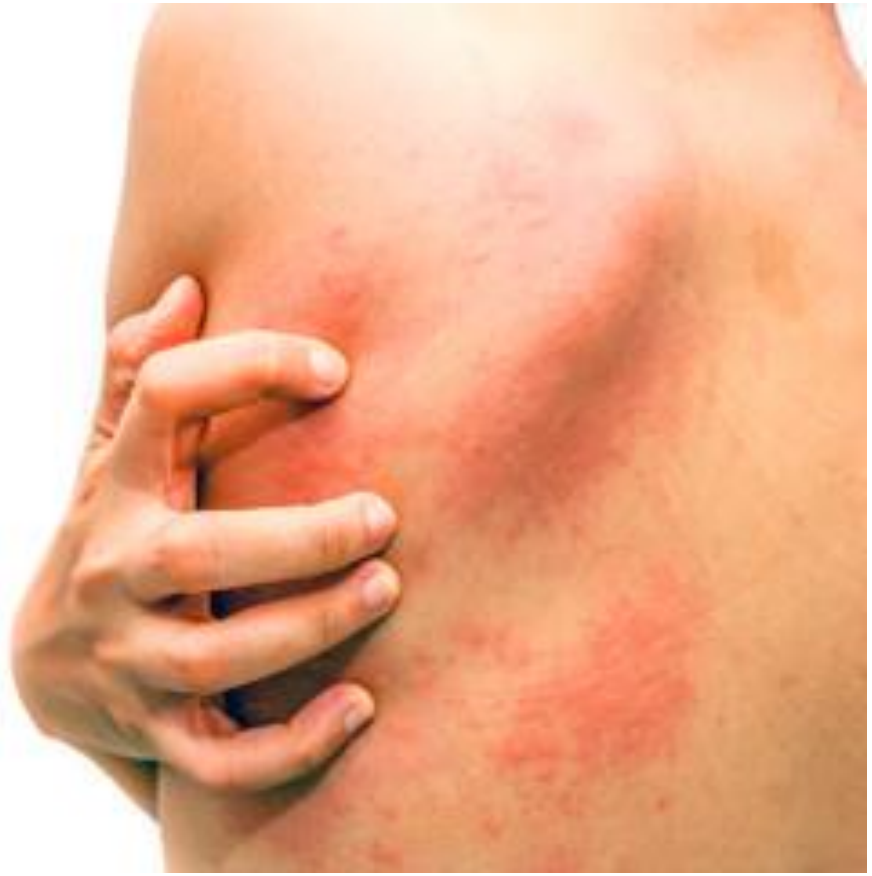
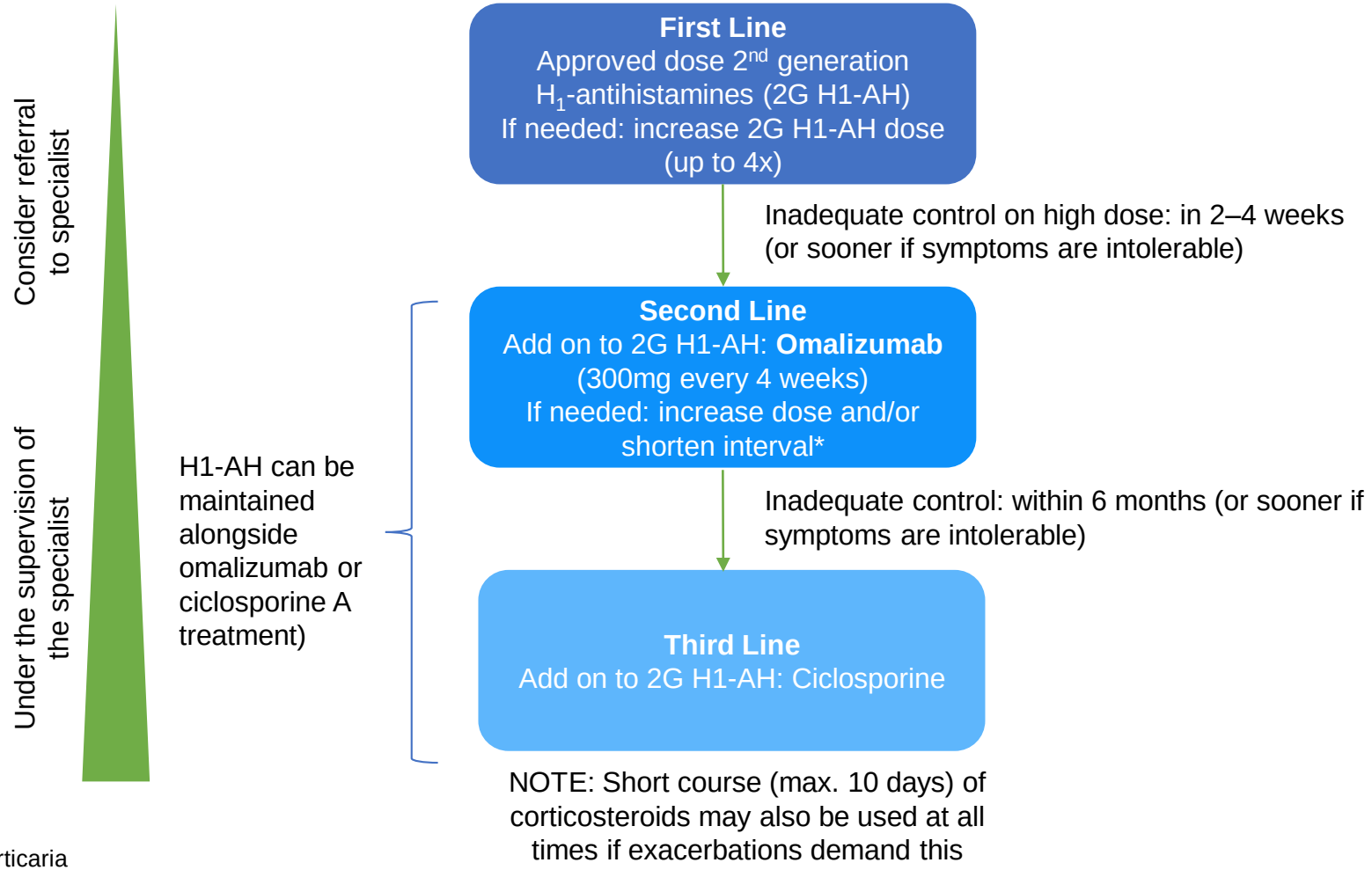
Orticaria cronica spontanea (CSU)

- Definita dalla presenza di pomfi e/o angioedema che si verificano per più di 6 settimane, senza un fattore scatenante specifico
- Condizione comune: che colpisce 0.5-1.5% della popolazione mondiale, con tendenza crescente nel tempo
- Lunga durata: (2 aa nel 60% dei casi, 5 anni nel 30% dei casi)
- Qualità di vita ridotta: per privazione del sonno, disfunzione sessuale, limitazioni nella vita quotidiana e prestazioni ridotte sul lavoro o a scuola
- Patogenesi oscura e mancanza di terapie specifiche, determinano **scarso controllo dei sintomi**



International guideline for CSU treatment



AH: antihistamine; CU: chronic urticaria

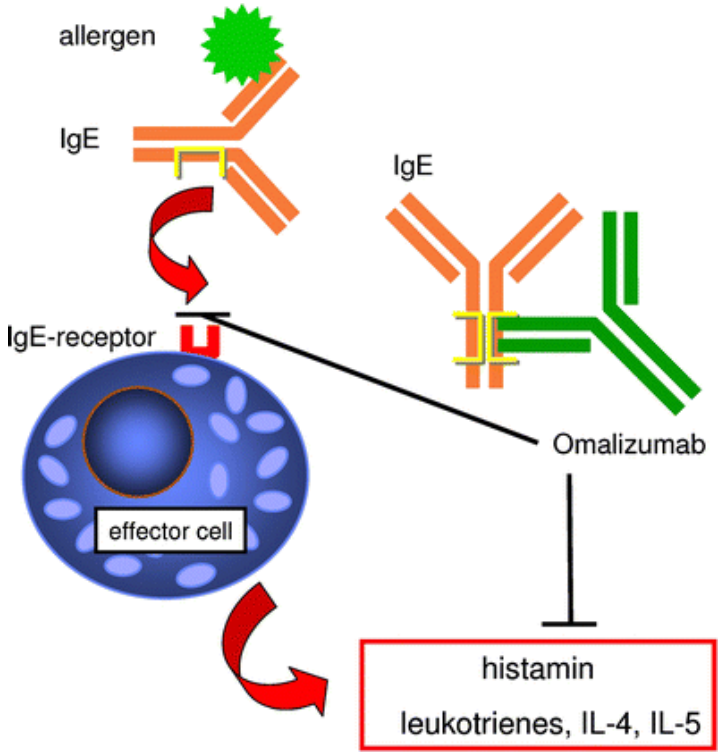
Zuberbier T, et al. Allergy. 2022 Mar;77(3):734-766

Antistaminici di seconda generazione (2G H1-AH)

- Somministrazione da circa 40 aa
- Uso associato ad alta efficacia sia a breve che a lungo termine
- Classi speciali: gravidanza/allattamento (loratadina/ebastina) e bambini (cetirizina, desloratadina, fenoxifenadina, levocetirizina, rupatadina, bilastina e loratadina)
- Fattori predittivi di mancata risposta: UAS7, D-dimero, PCR, VES e Paf elevati, eosinopenia, polimorfismi genici, concomitante CIndU

Mancata risposta: >50% dei pazienti

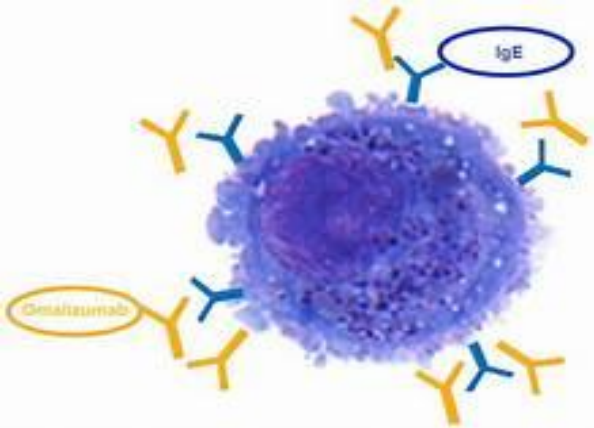
Principi di terapia- Omalizumab



Anticorpo monoclonale umanizzato IgG1k che si lega a IgE libere umane, rappresenta il primo biologico approvato per il trattamento CSU resistente a terapia antistaminica

Meccanismo d'azione:

- Legame alle IgE *libere* e inibizione dell'interazione recettoriale
- Downregolazione del recettore FcεF su mastociti, basofili e cellule presentanti l'antigene



Principi di terapia- Omalizumab

- Funziona in CSU e Orticaria Cronica Inducibile (CIndU)
- Riduzione di pomfi e angioedema
- Migliora la qualità della vita
- Adatto per il lungo-termine (6aa)
- Efficace nel trattare le recidive dopo interruzione
- Dosaggio standard (indipendente da IgE), che può variare in quantità, tempistica o entrambe
- Classi speciali: gravidanza/allattamento e bambini

Mancata risposta: >30% dei pazienti

Principi di terapia-Omalizumab

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VOLUME 137, NUMBER 6

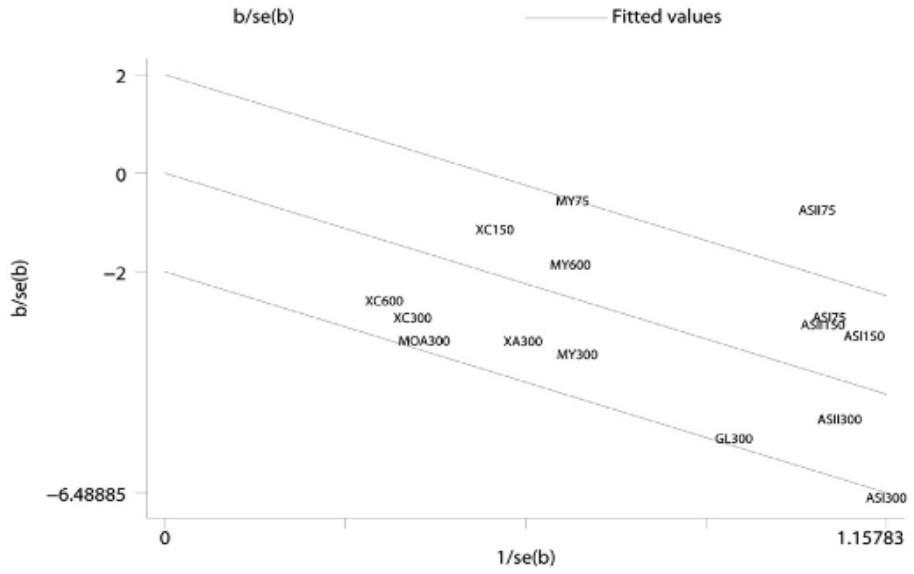

FIG 5. Galbraith radial plot. The figure shows the contribution of results from the patient groups treated with different doses of omalizumab in the different studies to the heterogeneity of efficacy of treatment. The group receiving 75 mg of omalizumab in the ASTERIA II study was found to be the main cause of the heterogeneity. *ASI75*, ASTERIA I 75 mg; *ASI150*, ASTERIA I 150 mg; *ASI300*, ASTERIA I 300 mg; *ASII75*, ASTERIA II 75 mg; *GL300*, GLACIAL 300 mg; *MOA300*, MOA 300 mg; *MY75*, MYSTQUE 75 mg; *MY300*, MYSTQUE 300 mg; *MY600*, MYSTQUE 600 mg; *XA300*, X-ACT 300 mg; *XC150*, XCUISITE 150 mg; *XC300*, XCUISITE 300 mg; *XC600*, XCUISITE 600 mg

Atopic dermatitis and skin disease

Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials

Zuo-Tao Zhao, MD, PhD,[a,d]* Chun-Mei Ji, M Pharm,[b]* Wen-Jun Yu, MD,[c]* Ling Meng, M Pharm,[b] Tomasz Hawro, MD,[d] Ji-Fu Wei, PhD,[b] and Marcus Maurer, MD[a,d] *Beijing and Nanjing, China, and Berlin, Germany*

Posologia: 1 fl. 150 mg x 2 ogni 15 giorni per 6 mesi – sospensione 8 settimane – eventuale prosecuzione ulteriori 6 mesi di terapia

Future Science OA

Improving of psychological status and inflammatory biomarkers during omalizumab for chronic spontaneous urticaria

Laura Diluvio*,[1], Arianna Piccolo[1], Francesco Marasco[2], Laura Vollono[1], Caterina Lanna[1], Barbara Chiaramonte[3], Cinzia Niolu[2], Elena Campione[1] & Luca Bianchi[1]
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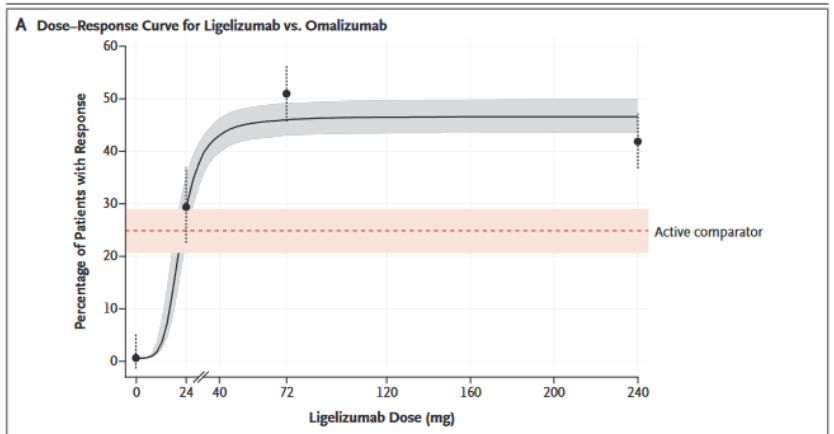
The NEW ENGLAND JOURNAL of MEDICINE

Terapie attuali

- Poco del 50% dei pazienti con CSU rispondono a una terapia H1-antistaminico a dosaggio standard, il trattamento di prima linea.
- Omalizumab, in uno studio comparativo di fase 2, ha mostrato a tasso di risposta completo del 26%, rispetto al 30%–51% a ligelizumab.
- Ciclosporina, dapsone, e l'idrossiclorochina sono utilizzati off-label.

ORIGINAL ARTICLE

Ligelizumab for Chronic Spontaneous Urticaria



B Response at Week 12

End Point, According to Treatment Group	Patients with Response no./total no. (%)	Odds Ratio (95% CI)
Weekly hives-severity score of 0		
Ligelizumab, 24 mg every 4 wk	13/43 (30)	1.22 (0.54–2.74)
Ligelizumab, 72 mg every 4 wk	43/84 (51)	2.90 (1.52–5.55)
Ligelizumab, 240 mg every 4 wk	36/85 (42)	2.06 (1.08–3.95)
Omalizumab, 300 mg every 4 wk	22/85 (26)	
Weekly itch-severity score of 0		
Ligelizumab, 24 mg every 4 wk	17/43 (40)	1.54 (0.71–3.33)
Ligelizumab, 72 mg every 4 wk	40/84 (48)	2.15 (1.14–4.06)
Ligelizumab, 240 mg every 4 wk	36/85 (42)	1.75 (0.92–3.31)
Omalizumab, 300 mg every 4 wk	25/85 (29)	
Weekly urticaria activity score of 0		
Ligelizumab, 24 mg every 4 wk	13/43 (30)	1.22 (0.54–2.75)
Ligelizumab, 72 mg every 4 wk	37/84 (44)	2.19 (1.14–4.19)
Ligelizumab, 240 mg every 4 wk	34/85 (40)	1.88 (0.98–3.61)
Omalizumab, 300 mg every 4 wk	22/85 (26)	

0.1 1.0 10.0
Omalizumab Better Ligelizumab Better

Endotipi CSU

Clinical reviews in allergy and clinical immunology

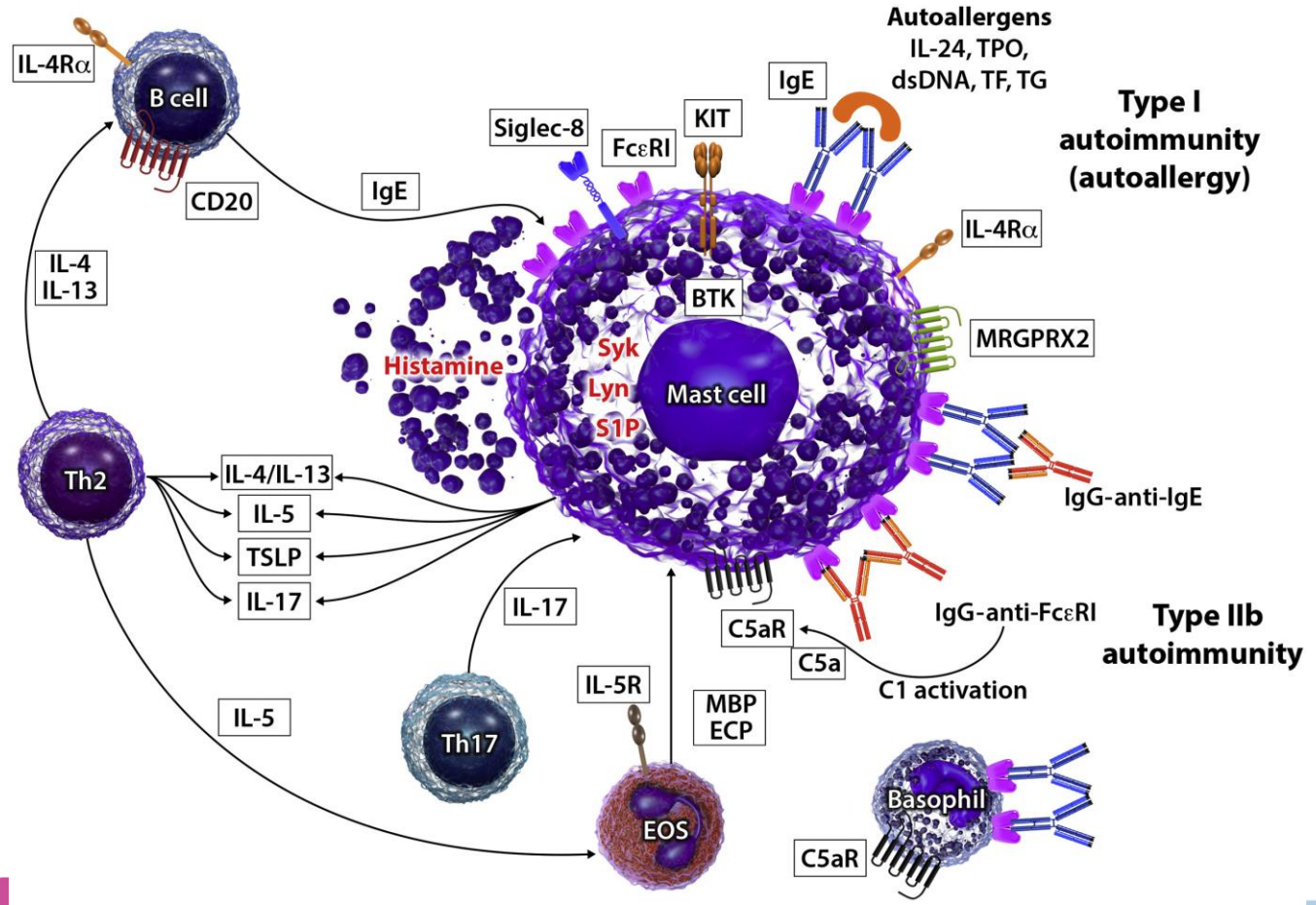
Autoimmune chronic spontaneous urticaria

Pavel Kolkhir, MD,[a,b,c]* Melba Muñoz, MD, PhD,[a,b,d]* Riccardo Asero, MD,[e] Marta Ferrer, MD, PhD,[f] Emek Kocatürk, MD,[g] Martin Metz, MD,[a,b] Yi-Kui Xiang, MD,[a,b] and Marcus Maurer, MD[a,b] *Berlin, Germany; Moscow, Russia; Paderno Dugnano, Italy; Madrid, Spain; and Istanbul, Turkey*

Tipo I della CSU autoallergica, caratterizzata da anticorpi IgE diretti agli auto-antigeni (chiamati anche autoallergeni)

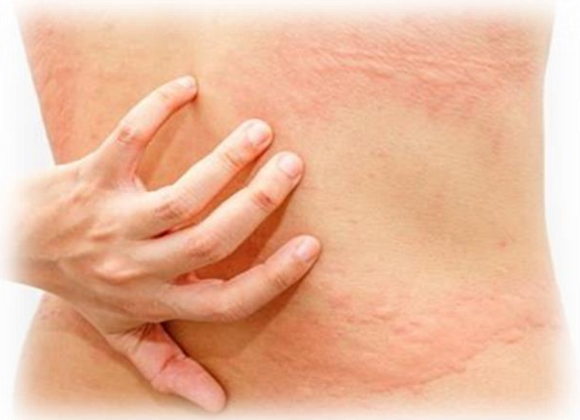
Tipo IIb, l'ipersensibilità è caratterizzata da un processo anticorpo-dipendente in cui anticorpi IgG specifici si legano agli autoantigeni

Una sovrapposizione tra i 2 endotipi sono stati recentemente segnalati



Endotipi CSU…..
…….STESSO FENOTIPO

*I due endotipi condividono la **manifestazione clinica** e **patogenesi** a valle dell'attivazione dei mastociti (vasodilatazione, stravaso, attivazione sensoriale nervosa, reclutamento delle cellule infiammatorie)*



- ***Tipo I della CSU autoallergica***
- *Più comune, associata ad allergie*
- *IgE anti TPO*
- *Risposta a omalizumab veloce e completa*
- ***Tipo tipo IIb***
- *10% dei pazienti, sesso femminile, malattie autoimmuni (tiroidite, vitiligine)*
- *Sintomi notturni, baso- e eosinopenia, bassi livelli di IgA, IgG anti TPO, bassi IgE*
- *CSU resistente e risposta a omalizumab e antistaminici scarsa; risposta buona a Cya*
- ***Miscellanea***

Terapie attuali ed emergenti per CSU

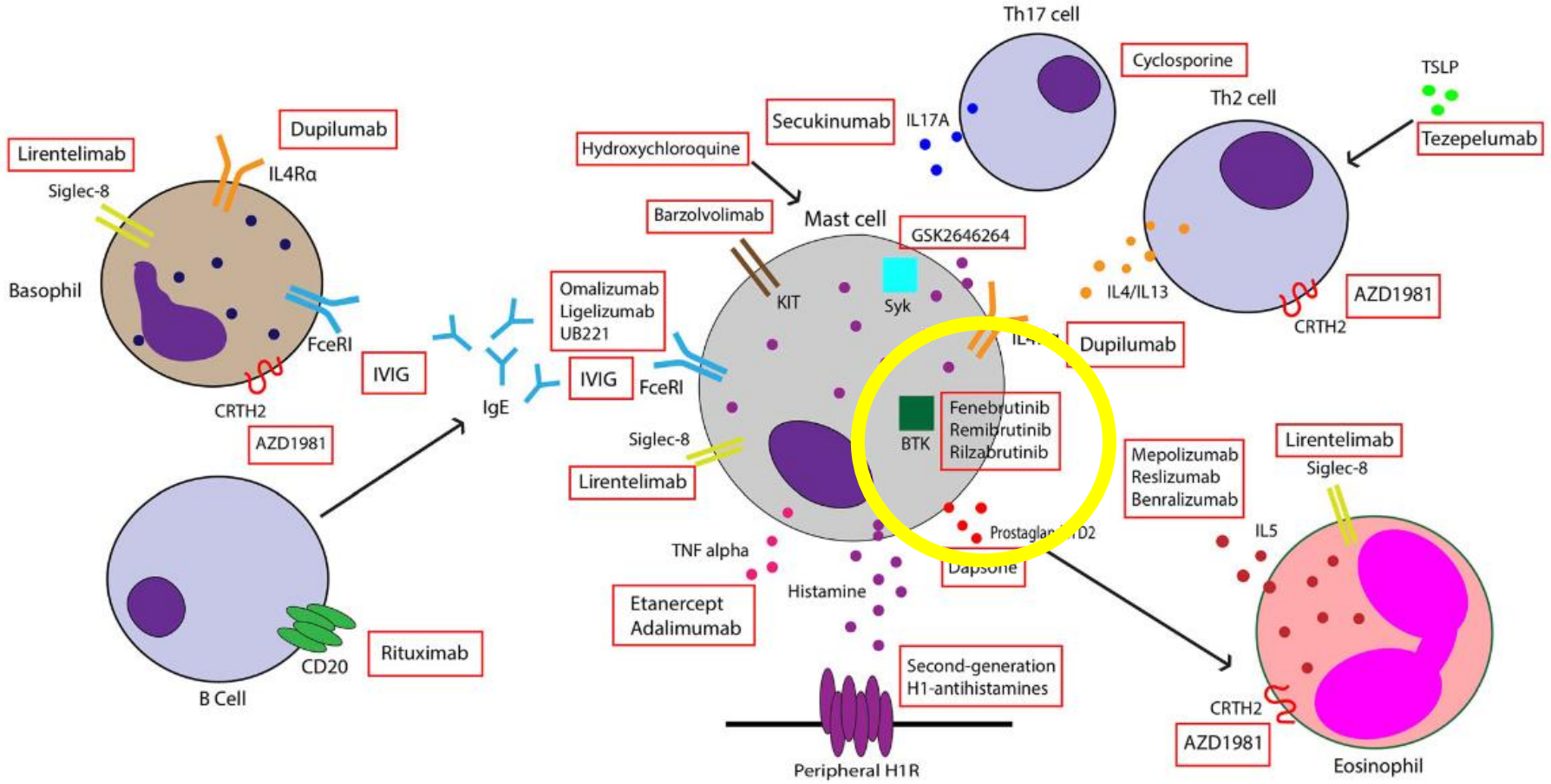
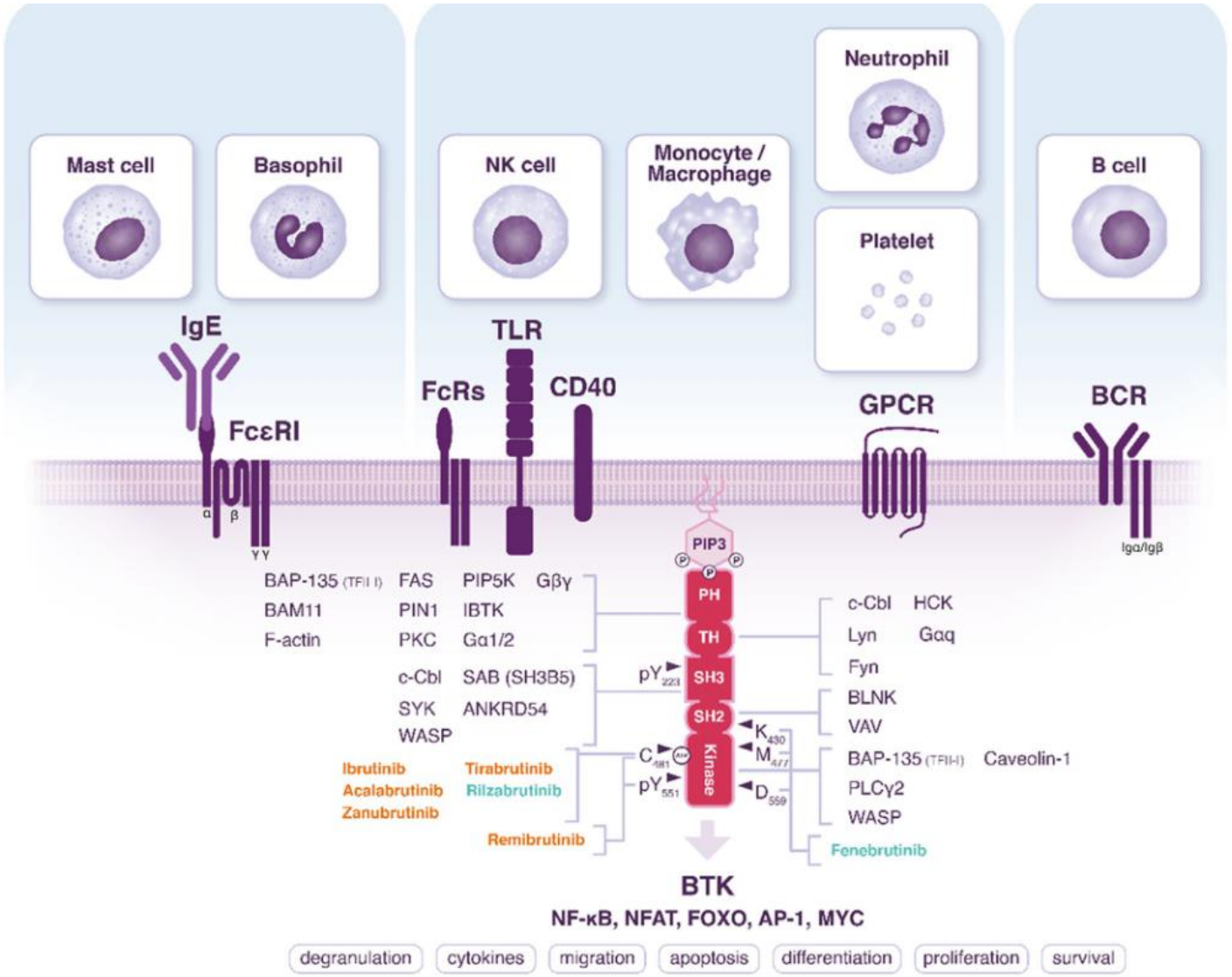


Fig. 1 Mechanism of action of some existing and novel therapies for chronic spontaneous urticaria

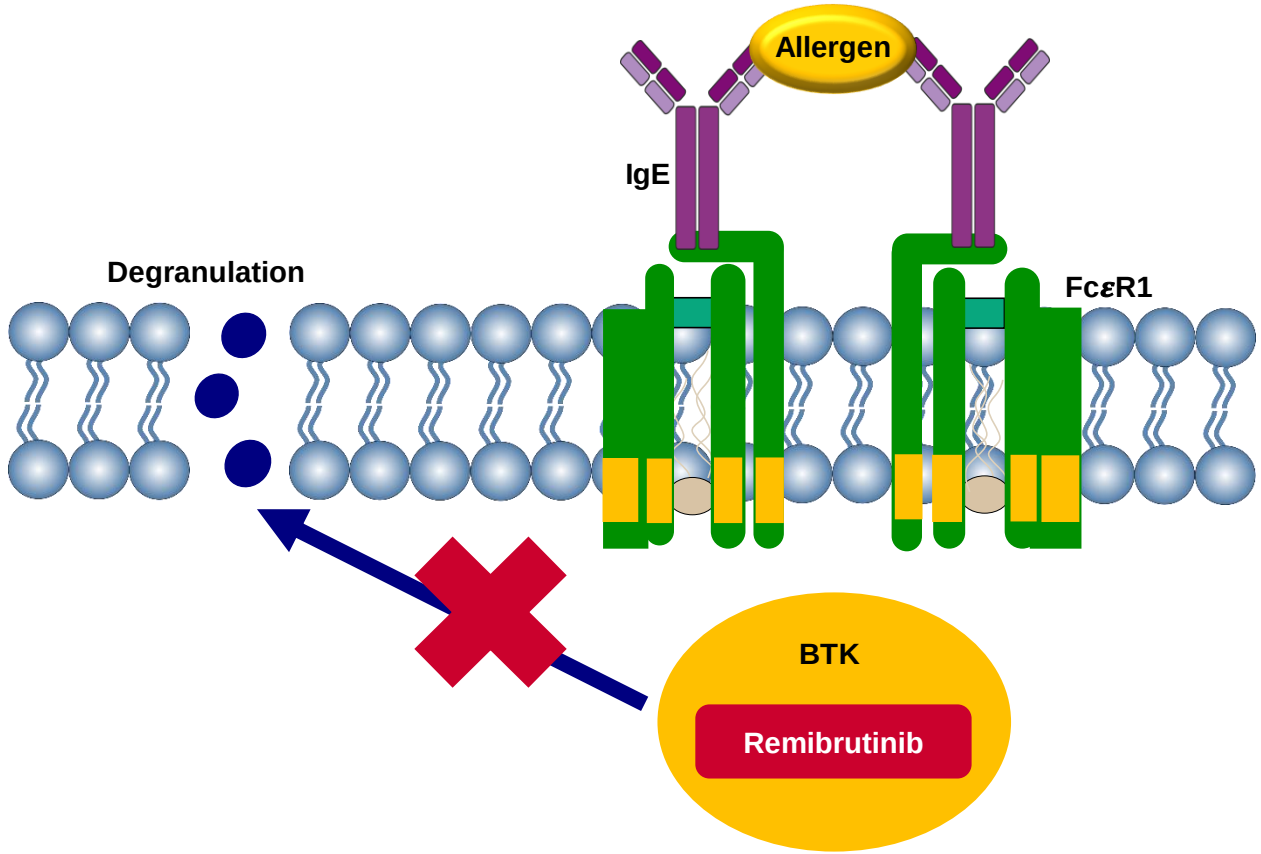
Cascata BTK in Cellule B e Mastociti



Remibrutinib (LOU064) is a novel, highly selective, potent, covalent, oral BTK inhibitor

Remibrutinib binds to BTK to block mast cell degranulation, regardless of the cause of FcεRI activation

- **Remibrutinib** enters the cell and **binds to BTK**, **suppressing** the downstream cascade of information and release of granule mediators including histamines and pro-inflammatory cytokines[1]
- **BTK** is also active on the **BCR,** hence, **inhibition of BTK** may lead to **lower** secretion/ production of antibodies including IgE in B cells[2]



CSU, chronic spontaneous urticaria; H1-AH, H1-antihistamines; RCT, randomized controlled trial; UAS7, weekly Urticaria Activity Score.
1. Maurer M, et al. *J Allergy Clin Immunol*. 2022; 150(6):1498–1506.e2; 2. Angst D, et al. *J Med Chem*. 2020;63:5102–5118.

BTK inhibitors have potential efficacy in both type I and type IIb CSU

1. Type I autoimmunity[1,2]
(also known as autoallergy)

- Type I autoantigens can activate mast cells and basophils by crosslinking IgE-AAbs

2. Type IIb autoimmunity[1,2]

- IgG-AAbs can activate mast cells and basophils by binding to IgE or to FcεRI, which might involve complement C5a and the CD88/C5aR receptor

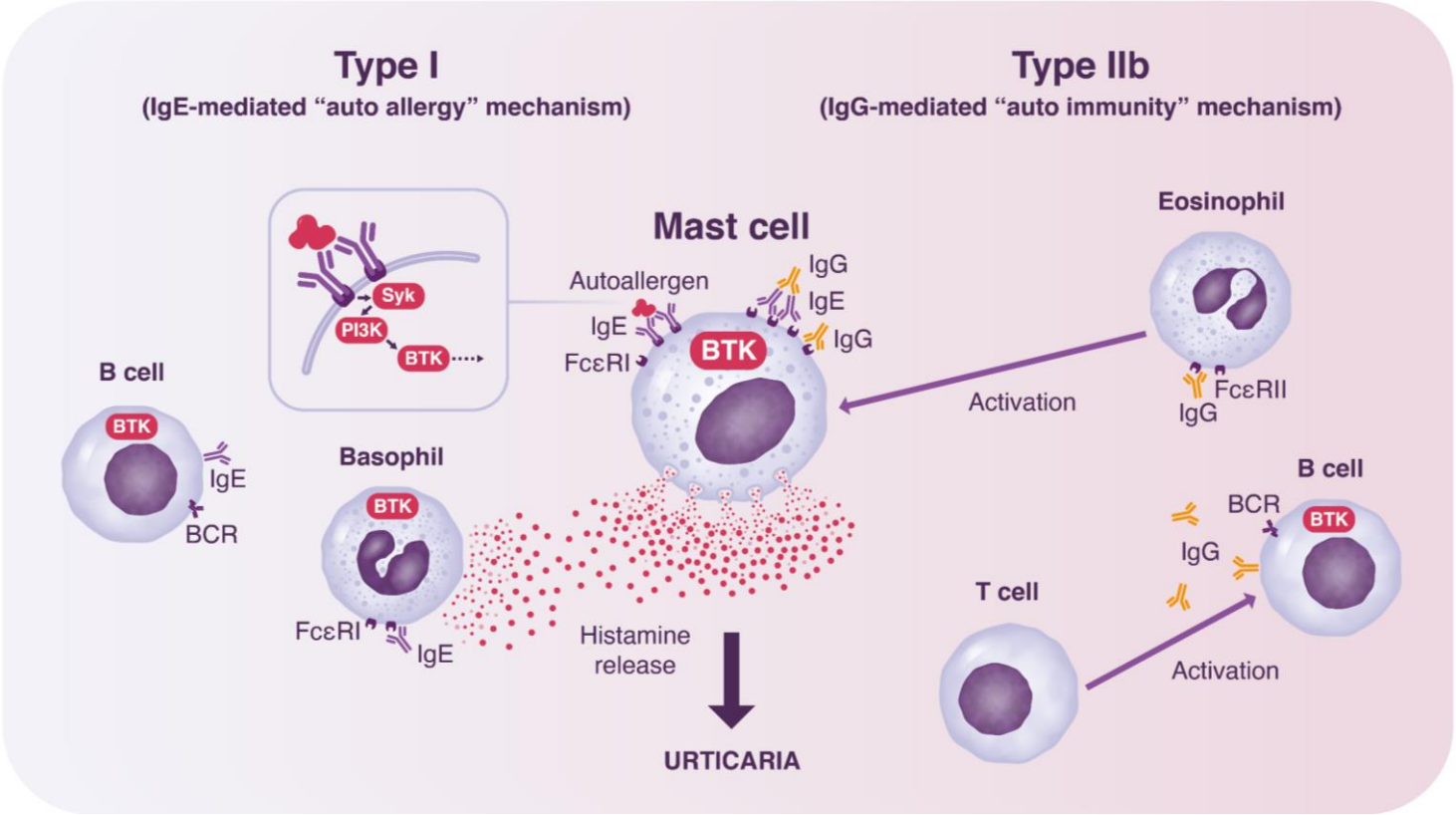


Figure source: Mendes-Bastos et al. Allergy. 2022;00(1):12

AAb, antithyroid autoantibody; CSU, chronic spontaneous urticaria; FcεRI, Fc epsilon RI; IgE, immunoglobulin E
1. Kolkhir P, et al. *J Allergy Clin Immunol*. 2017;139:1772–1778; 2. Maurer M, et al. *Int Arch Allergy Immunol*. 2020;181(5):321–333

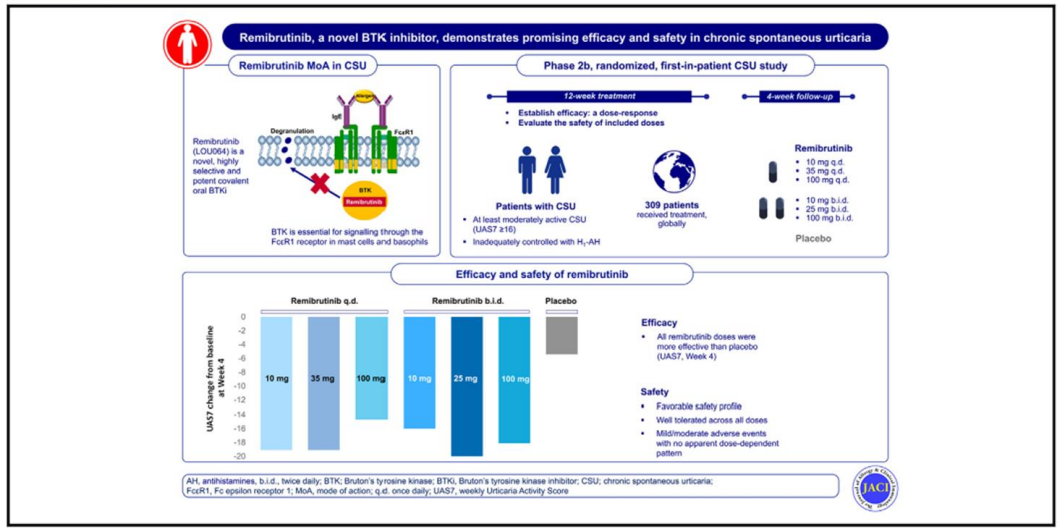
BCR, B cell receptor; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G; MC, mast cell. 1. Maurer M et al. World Allergy Organ J.2020;13(9):100460. 2. Maurer M et al. Allergy. 2017;72(12):2005-2016 3. Mendes-Bastos et al. Allergy. 2022;00(1):12

Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria

Marcus Maurer, MD,[a,b] William Berger, MD, MBA,[c] Ana Giménez-Arnau, MD,[d] Koremasa Hayama, MD,[e] Vipul Jain, MBBS, FRCPC,[f] Adam Reich, MD,[g] Sibylle Haemmerle, PhD,[h] Karine Lheritier, PhD,[h] Pauline Walsh, PhD,[i] Summer Xia, MSc,[j] and Julian Storim, PhD[h] *Berlin, Germany; Mission Viejo, Calif; Barcelona, Spain; Tokyo, Japan; Hamilton, Ontario, Canada; Rzeszów, Poland; Basel, Switzerland; Dublin, Ireland; and Shanghai, China*

Lo studio di fase 2b per la determinazione della dose ha dimostrato che remibrutinib è un trattamento efficace per la CSU nel complesso ***range di dosaggio*** testato (da 10 mg una volta al giorno a 100 mg due volte al giorno [b.i.d.]), con una rapida insorgenza d'azione e un profilo di sicurezza favorevole fino a 12 settimane in pazienti con CSU non adeguatamente controllata con antistaminici H

GRAPHICAL ABSTRACT



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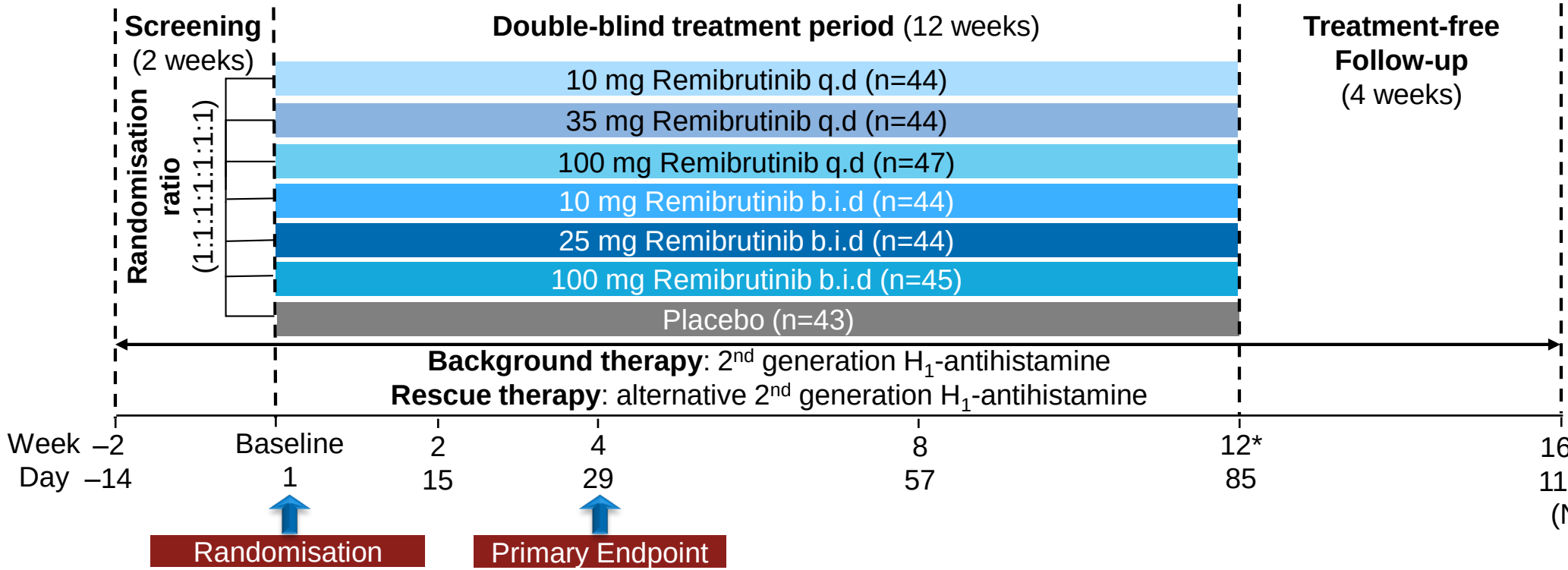
Study design: A dose-finding, multicenter, randomized, double-blind, placebo-controlled phase 2b study for up to 18 weeks



*Eligible patients rolled over into the extension study at Week 12 or at Week 16, following roll-over criteria defined in the extension study protocol and dependent of HAs/EC approval from participating countries. Background therapy was a 2nd generation H_1-antihistamine at a locally approved licensed posology that had to be administered daily with a stable treatment regimen throughout the study. Rescue therapy was a 2nd generation H_1-antihistamine at a locally approved licensed posology that differed from the background H_1-antihistamine, is eliminated primarily via renal excretion, and could only be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis
b.i.d., twice daily; CSU, chronic spontaneous urticaria; EC, ethics committee; HA, health authority; n, number of patients included in each group; q.d, once daily

(NCT03926611)

Primary objectives:

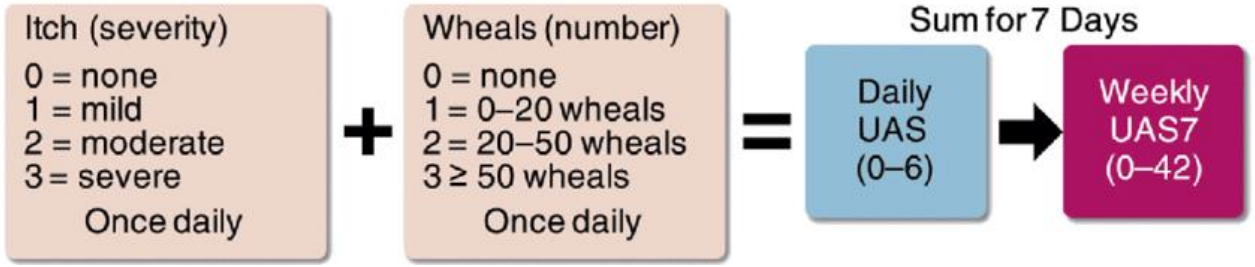
Efficacy and Safety of a range of remibutinib doses. The dose-response was investigated according to UAS7 change form baseline at week 4.

Key secondary endpoints: efficacy in terms of UAS7 change form baseline at week 12 and over the time and proportion of complete responde (UAS70) and well-controlled disease (UAS7<6)

Urticaria Activity Score (UAS)

- Sistema di punteggio basato sulla valutazione dell'intensità del prurito e del numero di pomfi
- Viene documentato *dal paziente*, una volta al giorno per sette giorni, rivelando l'attività di malattia durante la settimana
- La somma dei punteggi crea l'UAS settimanale (UAS7) con un punteggio fra 0-42.
- I punteggi UAS7 vengono quindi classificati in intervalli che descrivono gli stati di salute della CSU
- Recentemente è stata introdotta la misura del pomfo più largo (0-3 [>2,5 cm])

Score	Wheals	Itch
0 None	None	None
1 Mild	<20 wheals/24 h	Mild (present, but not annoying or troublesome)
2 Moderate	20–50 wheals/24 h	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3 Intense	>50 wheals/24 h or large confluent areas of wheals	Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)



The EAACI/GA 2 LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Zuberbier, et al, Allergy 2014
Miynek.A. Allergy 2008

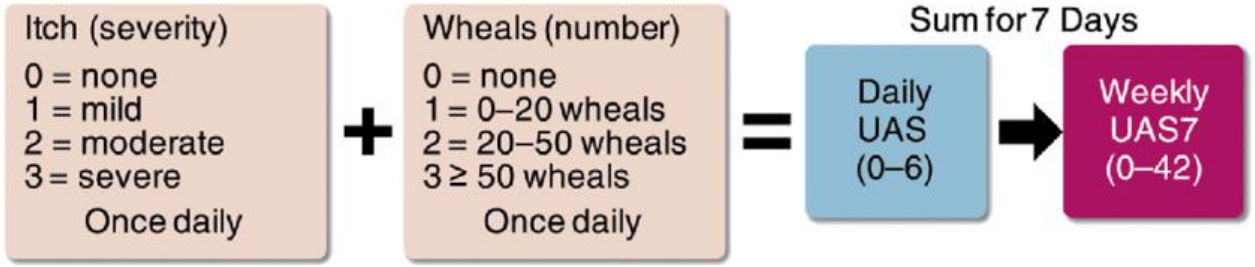
Urticaria Activity Score

Strumento utile e valido per misurare l'***attività*** di malattia e la r**isposta** alla terapia in pazienti con CSU (follow-up e monitoraggio) nei trial e pratica clinica

Limiti maggiori:

- Strumento prospettico
- Dimenticanza da parte del paziente
- Non include angioedema
- Specifico per CSU
- Non misura il controllo della malattia

Score	Wheals	Itch
0 None	None	None
1 Mild	<20 wheals/24 h	Mild (present, but not annoying or troublesome)
2 Moderate	20–50 wheals/24 h	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3 Intense	>50 wheals/24 h or large confluent areas of wheals	Intense (severe itching, which is sufficiently troublesome to interfere with normal daily activity or sleep)



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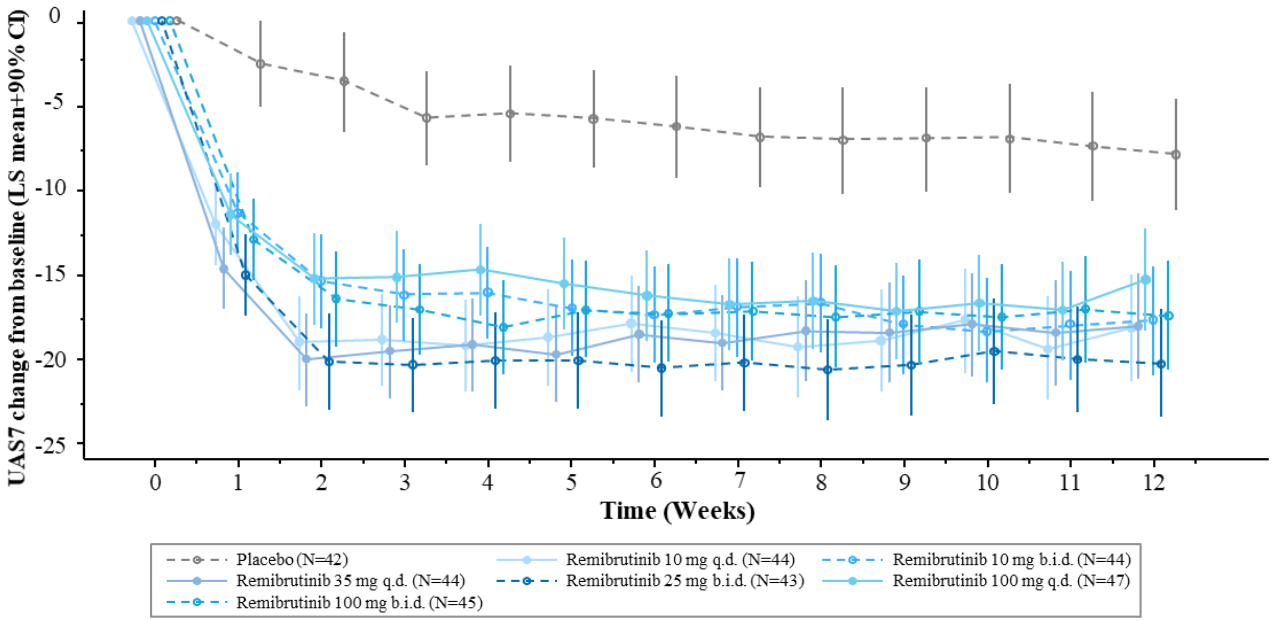
Miynek.A. Allergy 2008

Remibrutinib showed rapid and significant improvement in baseline UAS7 up to 12 week vs. placebo



Change from baseline in UAS7 at Week 12 for each study arm	
Treatment arm	**LS mean change (SE)**
Remibrutinib 10 mg q.d. (N=44)	-18.1 (1.9)
Remibrutinib 35 mg q.d. (N=44)	-18.0 (1.9)
Remibrutinib 100 mg q.d. (N=47)	-15.3 (1.9)
Remibrutinib 10 mg b.i.d. (N=44)	-17.7 (1.9)
Remibrutinib 25 mg b.i.d. (N=43)	-20.2 (2.0)
Remibrutinib 100 mg b.i.d. (N=45)	-17.4 (2.0)
Placebo (N=42)	-7.9 (2.0)

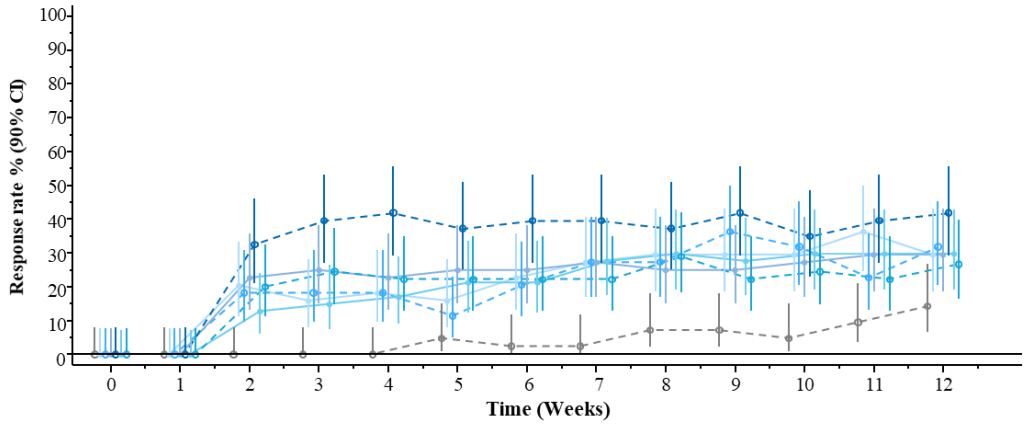
- UAS7 improved from baseline up to Week 12 in **all remibrutinib doses** compared with placebo
- A rapid improvement in UAS7 was observed as early as at Week 1, which was maintained up to Week 12

b.i.d., twice daily; CI, confidence interval; LS, least squares; N, number of patients; q.d., once daily; SE, standard error; UAS7, weekly Urticaria Activity Score

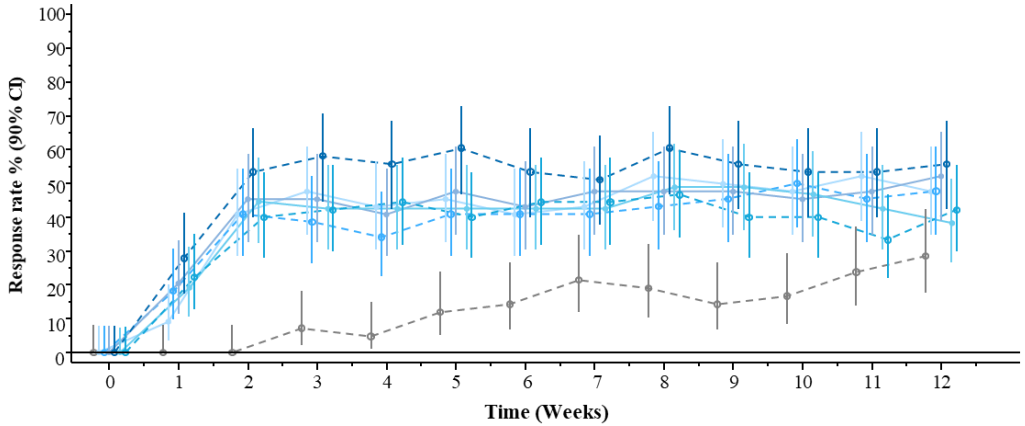
Maurer M. et al J Allergy Clin Immunol. 2023 Feb;151(2):579

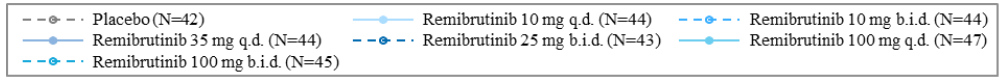
More patients achieved UAS7=0 and UAS7≤6 with remibrutinib doses vs. placebo up to Week 12

Complete response (UAS7=0) over time during the treatment period (non-responder imputation)



Well-controlled disease response (UAS7≤6) over time during the treatment period (non-responder imputation)





- Compared with placebo, more patients receiving any remibrutinib dose achieved a complete absence of hives and itch (UAS7=0) and well-controlled disease response (UAS7≤6) over the 12-week treatment period
- From Week 2, these responses were maintained (UAS7≤6) or gradually increased further (UAS7=0) up to Week 12

b.i.d., twice daily; CI, confidence interval; mg, milligram; N, total number of patients; q.d., once daily; UAS7, weekly Urticaria Activity Score

Maurer M. et al J Allergy Clin Immunol. 2023 Feb;151(2):579

Remibrutinib had a favorable safety profile across the entire dose range

- Remibrutinib had a favorable safety profile across all doses, with no apparent dose –dependent pattern
- 58.1% (155/267) of patients receiving any remibrutinib dose reported at least 1 AE (mild-38%, moderate-16%, severe-2% of patients)

TABLE III. Safety summary of treatment-emergent AEs, serious AEs, and exposure

Characteristic	Remibrutinib 10 mg q.d. (n = 44)	Remibrutinib 35 mg q.d. (n = 44)	Remibrutinib 100 mg q.d. (n = 47)	Remibrutinib 10 mg b.i.d. (n = 44)	Remibrutinib 25 mg b.i.d. (n = 43)	Remibrutinib 100 mg b.i.d. (n = 45)	Remibrutinib Any (n = 267)	Placebo (n = 42)
Duration of exposure ≥12 weeks	38 (86.4)	38 (86.4)	39 (83.0)	37 (84.1)	38 (88.4)	31 (68.9)	221 (82.8)	34 (81.0)
Patient-year	10.1	10.1	10.9	9.8	9.8	9.3	59.9	9.5
Patients with serious AE(s)	1 (2.3)	0	0	2 (4.5)	2 (4.7)	0	5 (1.9)	0
Lymphadenopathy (PT)	1 (2.3)	0	0	0	0	0	1 (0.4)	0
Renal abscess (PT)	0	0	0	0	1 (2.3)	0	1 (0.4)	0
Ureterolithiasis (PT)	0	0	0	1 (2.3)	0	0	1 (0.4)	0
CSU (PT)	0	0	0	1 (2.3)	1 (2.3)	0	2 (0.7)	0
Patients with at least 1 AE	29 (65.9)	23 (52.3)	27 (57.4)	21 (47.7)	26 (60.5)	29 (64.4)	155 (58.1)	18 (42.9)
Mild	22 (50.0)	16 (36.4)	18 (38.3)	9 (20.5)	16 (37.2)	22 (48.9)	103 (38.6)	14 (33.3)
Moderate	7 (15.9)	6 (13.6)	8 (17.0)	10 (22.7)	9 (20.9)	5 (11.1)	45 (16.9)	4 (9.5)
Severe	0	1 (2.3)	1 (2.1)	2 (4.5)	1 (2.3)	2 (4.4)	7 (2.6)	0
AEs by PT (≥5% in any treatment group)								
Headache	1 (2.3)	7 (15.9)	4 (8.5)	3 (6.8)	6 (14.0)	5 (11.1)	26 (9.7)	6 (14.3)
Nasopharyngitis	7 (15.9)	2 (4.5)	2 (4.3)	4 (9.1)	4 (9.3)	4 (8.9)	23 (8.6)	3 (7.1)
CSU	3 (6.8)	2 (4.5)	3 (6.4)	4 (9.1)	2 (4.7)	2 (4.4)	16 (6.0)	1 (2.4)
Nausea	2 (4.5)	3 (6.8)	1 (2.1)	1 (2.3)	1 (2.3)	2 (4.4)	10 (3.7)	0
Upper respiratory tract infection	1 (2.3)	2 (4.5)	2 (4.3)	0	3 (7.0)	0	8 (3.0)	1 (2.4)
Diarrhea	2 (4.5)	0	0	4 (9.1)	0	1 (2.2)	7 (2.6)	2 (4.8)
Pyrexia	3 (6.8)	0	0	2 (4.5)	1 (2.3)	0	6 (2.2)	0
Discontinued study treatment due to AE(s)	0	0	0	3 (6.8)	1 (2.3)	3 (6.7)	7 (2.6)	0
AEs by primary system organ class (≥10% of all patients receiving any remibrutinib dose)								
Infections and infestations	12 (27.3)	9 (20.5)	14 (29.8)	6 (13.6)	12 (27.9)	11 (24.4)	64 (24.0)	9 (21.4)
Skin and subcutaneous tissue disorders	7 (15.9)	9 (20.5)	5 (10.6)	6 (13.6)	12 (27.9)	6 (13.3)	45 (16.9)	2 (4.8)
Nervous system disorders	3 (6.8)	10 (22.7)	7 (14.9)	4 (9.1)	6 (14.0)	5 (11.1)	35 (13.1)	7 (16.7)
Gastrointestinal disorders	7 (15.9)	4 (9.1)	6 (12.8)	6 (13.6)	2 (4.7)	5 (11.1)	30 (11.2)	5 (11.9)
Investigations	6 (13.6)	4 (9.1)	6 (12.8)	2 (4.5)	4 (9.3)	3 (6.7)	25 (9.4)	3 (7.1)
Musculoskeletal and connective tissue disorders	4 (9.1)	1 (2.3)	3 (6.4)	3 (6.8)	7 (16.3)	6 (13.3)	24 (9.0)	2 (4.8)

Data are presented as nos. (%) unless otherwise indicated. Medical Dictionary for Regulatory Activities, version 24.0, was used for reporting. *b.i.d.*, Twice daily; *n*, number of patients; *PT*, preferred term; *q.d.*, once daily.

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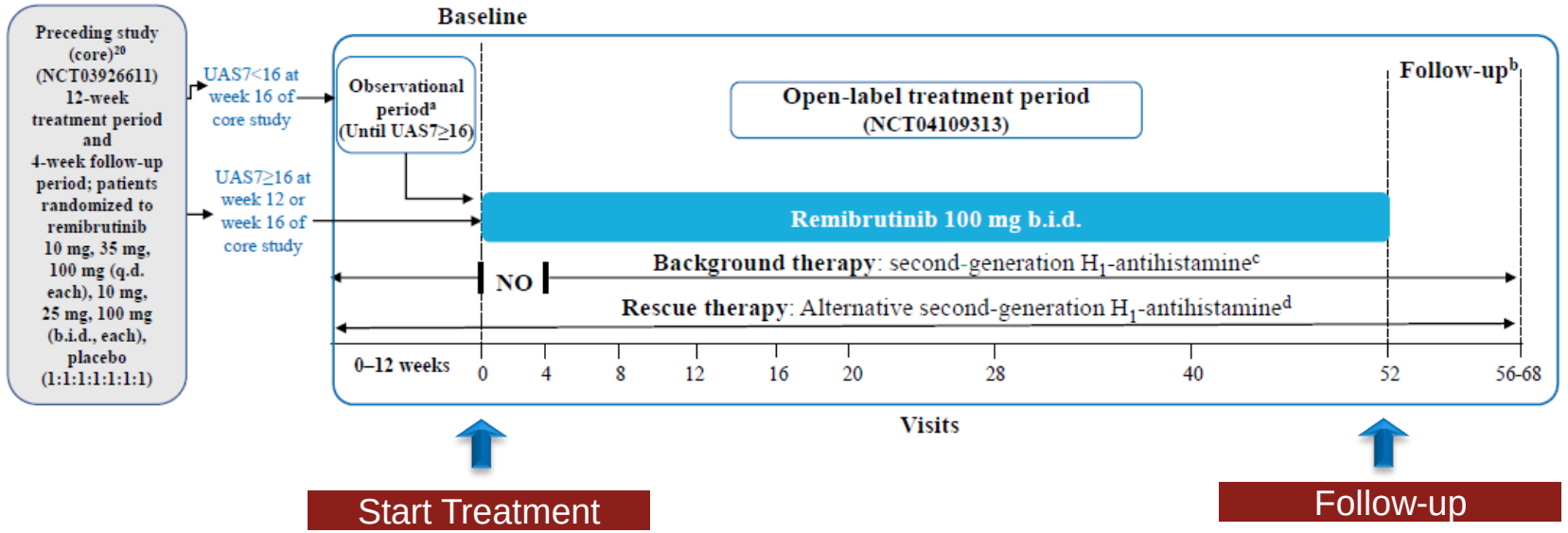
Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks



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Primary objectives:

Safety, occurrence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs).

Efficacy, change from baseline in UAS7 and the proportion of patients achieving complete response to treatment (UAS7 =0) and well-controlled disease (UAS7 <6) at week 4 (no background H1 antihistamine was allowed up to week 4) and over time up to 52 weeks.

- UAS7 values range from 0 to 42, with higher scores indicating greater severity

Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks

Change from baseline in UAS7 at week 4 and over time. At week 4, the mean change from baseline in UAS7 was -17.6, in the absence of background H1 antihistamine medication, which was not permitted up to week 4 of the treatment period. Clinical improvement was rapid, with reductions in UAS7 from baseline as early as week 1 (-14.8) that continued to decrease until week 52

Complete response at week 4 and over time. Complete response *(UAS7=0)* was achieved in *27.3%* of patients at week 4; UAS7=0 response was 28.2% at week 4 and 43.4% at week 12 and continued to increase further, with *55.8%* of patients achieving a complete response at week 52

Well-controlled disease response at week 4 and over time. Well-controlled disease response *(UAS7 <6)* was achieved in *51.0%* of patients at week 4, the UAS7 <6 response increased further and was maintained through week 52 .

Primary Endpoint

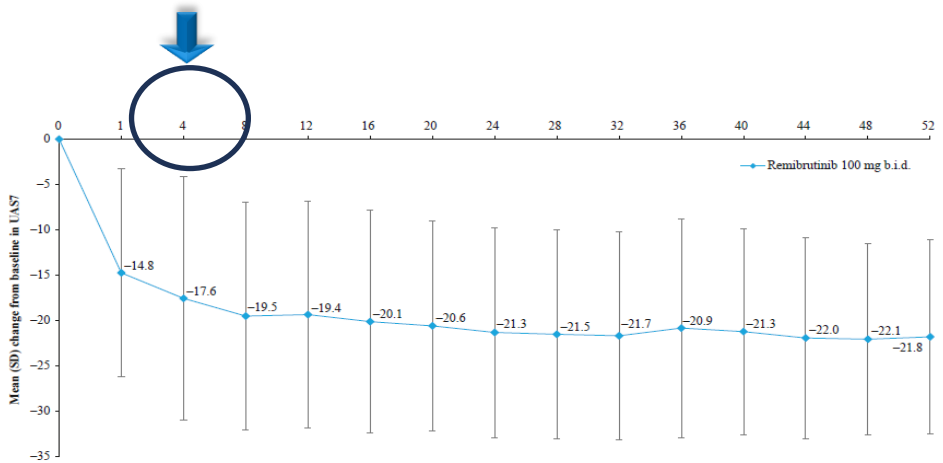
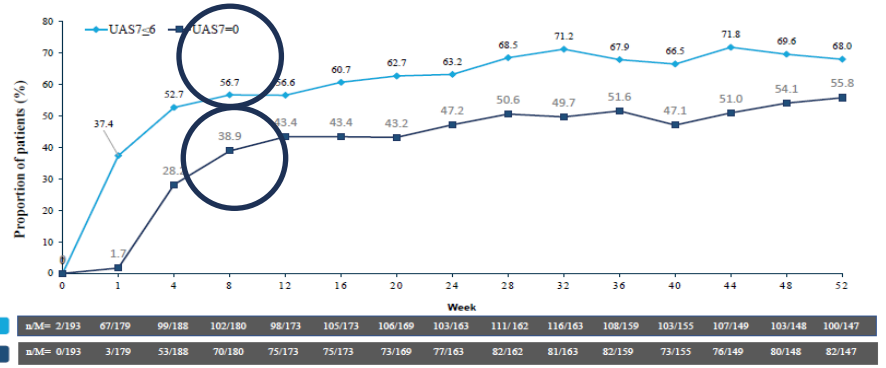


FIG 3. Change from baseline in UAS7 during treatment period (as observed; safety set). n, number of patients with assessment at the specified time point.



UAS7≤6	n/M= 2/193	67/179	99/188	102/180	98/173	105/173	106/169	103/163	111/162	116/163	108/159	103/155	107/149	103/148	100/147
UAS7=0	n/M= 0/193	3/179	53/188	70/180	75/173	75/173	73/169	77/163	82/162	81/163	82/159	73/155	76/149	80/148	82/147

FIG 4. UAS7 = 0 and UAS7 ≤6 response rates over time during treatment period (as observed; safety set). *M*, Number of patients evaluable; *n*, number of patients with assessment at the specified time point.

Jain V, et al. J Aller Clin Immunol 2023 in press

Remibrutinib demonstrates favorable safety profile and sustained efficacy in chronic spontaneous urticaria over 52 weeks

Overall safety. Overall, 71.6% (139/194) of patients reported at least 1 TEAE. *The majority of TEAEs were mild to moderate*, with 35.1% (68/194) of patients reporting at least one mild or moderate. Severe events were reported in 4.1% (8/194) of patients and included CSU and upper abdominal pain, appendicitis, COVID-19 pneumonia, muscle strain, muscle spasms, osteonecrosis, and nephrolithiasis

Laboratory investigations and vital signs: no significant findings

Change in immunoglobulin levels: changes from baseline in total serum levels of IgE, IgA, IgG, and IgM observed over time with remibrutinib

11% patients **discontinued study treatment** due to SAEs

No deaths occurred in the study.

TABLE II. Summary of clinically significant adverse events or related discontinuations—treatment period (safety set) (N = 194)

	Remibrutinib 100 mg b.i.d.
Duration of exposure, wk, median (Q1-Q3)	52.1 (51.6-52.4)
Patients with at least 1 TEAE, no. (%)	139 (71.6)
Patients with treatment-emergent SAE(s), no. (%)	6 (3.1)
Discontinued study treatment due to TEAE(s)/SAE(s), no. (%)	11 (5.7)
Death, no. (%)	0 (0.0)

N, total number of patients; *no.*, number of patients in each category; *Q1-Q3*, interquartile range.

TABLE III. Most frequent TEAEs by primary system organ class and preferred term—treatment period (safety set) (N = 194)

	Remibrutinib 100 mg b.i.d., no. (%)
TEAEs by primary system organ class*	
Infections and infestations	60 (30.9)
Skin and subcutaneous tissue disorders	52 (26.8)
Gastrointestinal disorders	32 (16.5)
Musculoskeletal and connective tissue disorders	26 (13.4)
Nervous system disorders	23 (11.9)
Injury, poisoning, and procedural complications	21 (10.8)
General disorders and administration site conditions	20 (10.3)
TEAEs by preferred term†	
Chronic spontaneous urticaria	22 (11.3)
COVID-19	16 (8.2)
Headache	13 (6.7)
Eczema	10 (5.2)

Adverse events occurring during treatment or within 28 days of the last study medication are summarized. MedDRA Version 25.0 (www.meddra.org) was used for reporting of adverse events. *AE*, Adverse event; *COVID-19*, coronavirus disease; *N*, total number of patients; *no.*, number of patients in each category.
*Occurring in ≥10% of patients.
†Occurring in ≥5% of patients.

Conclusioni

- Il profilo di sicurezza e tollerabilità e l’efficacia prolungata con remibrutinib 100 mg bid per 52 settimane supportano lo sviluppo del farmaco in pazienti con CSU non controllata con antistaminici
- Remibrutinib potrebbe quindi essere una nuova opzione di trattamento orale, per il rapido controllo della malattia e il profilo di sicurezza favorevole
- Gli studi clinici di fase 3 mirano a confermare e valutare ulteriormente l’efficacia e la sicurezza di remibrutinib in pazienti adulti affetti da CSU

Grazie