Redefining patient care in chronic spontaneous urticaria

EADV virtual symposium
Friday 30th October 2020, 8:30-9:30 CET

This meeting is sponsored by Novartis Pharma AG
Ligelizumab is an investigational drug in development in development for CSU
Zinc number: GLDEIM/QGE031C/0037b
Recording Zinc number: GLDEIM/QGE031C/0037f
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Housekeeping

Please use the chat function to submit questions to the faculty. Questions will be addressed during the Q&A discussion.

The recording will be available to watch after the virtual symposium.
## Agenda

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<th>Duration</th>
<th>Title</th>
<th>Speaker</th>
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<td>5 min.</td>
<td>Welcome &amp; Introduction</td>
<td>Marcus Maurer (Chair)</td>
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<td>15 min.</td>
<td>Be AWARE – learnings from real world evidence</td>
<td>Ana Giménez-Arnau</td>
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<td>15 min.</td>
<td>IgE inhibition in CSU: not all anti-IgEs are born equal</td>
<td>Alexander Eggel</td>
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<td>15 min.</td>
<td>IgE implications: How does this benefit patients with CSU?</td>
<td>Marcus Maurer</td>
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<td>10 min.</td>
<td>Live Q&amp;A (Speakers will also answer questions through the chat during the symposium session)*</td>
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*you can also ask question during the symposium by using the chat function
Ana M Giménez-Arnau is a professor of Dermatology at the Universitat Autònoma of Barcelona and Consultant Physician in Dermatology and Venereology in the Hospital del Mar.

Dr. Giménez-Arnau is the author of 216 international and 250 national peer-reviewed scientific publications, as well as textbooks on contact dermatitis, atopic dermatitis, urticaria, and therapy in dermatology. She is a member of at least 15 scientific associations, including the European Society of Contact Dermatitis (secretary from 2007 to 2012), European Society for Dermatology Research, European Academy of Dermatology, European Academy of Allergy and Clinical Immunology (past member of the Dermatology Board), and American Academy of Dermatology.

Dr. Gimenez-Arnau received her degree in Medicine and Surgery and completed her doctorate training (cum laude) at the Autonomous University of Barcelona. She is board certified in dermatology and venereology. Her main research interests include urticaria and eczema, as well as contact dermatitis and atopic dermatitis.
Alexander Eggel is a principal investigator at the Department of Rheumatology, Immunology and Allergy at the University Hospital Bern in Switzerland.

Dr Eggel obtained his PhD degree at University of Bern in Switzerland and following postdoctoral training at the University of Stanford, he returned to Bern and is currently an independent Research Group Leader at the Department of Rheumatology, Immunology and Allergology.

PD Dr Eggel is the Principal Investigator at the Eggel Lab of Immunology Research. His major research interests focus on the biologic mechanisms underlying both beneficial, as well as, pathologic type 2 immune responses. He has authored over 20 publications in peer-reviewed journals, including the recent Nature Communications paper reviewing anti-IgE antibody profiles. Over the years, he has received recognition for outstanding work in the fields of allergy and immunology.
Marcus Maurer is Professor of Dermatology and Allergy, Head of Dermatological Allergology and Director of Research at the Department of Dermatology and Allergy and the Allergie-Centrum-Charité, Charité - Universitätsmedizin Berlin. He is also Head of the Specialty Clinics for Urticaria, Mastocytosis, Pruritus and Angioedema and the Dermatological Allergology Lab.

Prof. Maurer is a Dermatologist and Allergologist, and also trained in experimental pathology at the Beth Israel Deaconess Hospital and Harvard Medical School in Boston, with Board certification for Dermatology and Allergology. He was an Assistant Professor at the Allergie-Centrum-Charité at Charité – Universitätsmedizin Berlin (2004-2005). Since 2005, Prof. Maurer has been a full professor at Charité and coordinator of the GA²LEN urticaria centers of reference and excellence (UCARE) network.

Prof. Maurer is a coordinator of the National Priority Programme “Physiological functions of mast cells”, chair of the World Allergy Organization (WAO) skin allergy committee and has >557 publications in peer-review journals (h-index: 98; > 40953 citations; IF > 3060), 40 books and book chapters. His scientific areas of interest include characterization of physiological functions of mast cells, neuroimmunology, inflammation, innate immunity, tolerance.
Introduction – Redefining patient care in chronic spontaneous urticaria

Marcus Maurer
Allergie-Centrum-Charité of the Charité - Universitätsmedizin

This meeting is sponsored by Novartis Pharma AG
Ligelizumab is an investigational drug in development for the treatment of CSU and has not received marketing authorization
Zinc number: GLDEIM/QGE031C/0037b
Disclosures

- Marcus Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Araelez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, MSD, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach.
CSU is a debilitating and chronic disease

CSU is the sudden appearance of hives and/or angioedema for at least 6 weeks, with no definite trigger

Mast cells are the primary effector cells responsible for clinical symptoms

Worldwide prevalence is approximately 0.5–1%3–5

CSU can be difficult to treat, and frustrating for both patients and physicians

CSU has a significant impact on patients and places a high burden on society

CSU, chronic spontaneous urticaria.
**Mast cell activation by auto antigen cross-linking of FcεRI-bound IgE**

Type I autoimmune response (autoallergic)
- Crosslinking induced by auto antigen recognized by IgE (up to 50% of patients)

**CAUSE**
- Crosslinking induced by auto antigen
- Crosslinking recognized by IgE

**Symptoms**
- Itch
- Hives
- Angioedema

**Effect**
- Activation triggers a cascade of reactions inside the cell


CSU, chronic spontaneous urticaria; CU, chronic urticaria; FcεRI, high affinity IgE receptor; IgE, immunoglobulin E; IgG, immunoglobulin G
**Mast cell activation by IgG anti-FcεRI cross-linking of FcεRI**

Type IIb autoimmune response

- Crosslinking induced by IgG anti FcεRI (35-40% of patients)

**CSU SYMPTOMS: ITCH, HIVES, ANGIOEDEMA**

CSU, chronic spontaneous urticaria; CU, chronic urticaria; FcεRI, high affinity IgE receptor; IgE, immunoglobulin E; IgG, immunoglobulin G

**3 Mast cell activation by IgG anti-IgE cross-linking FcεRI-bound IgE**

Type IIb autoimmune response

- Crosslinking induced by IgG anti FcεRI (35-40% of patients)
  - Crosslinking induced by IgG anti-IgE (5–10% of patients)

CSU SYMPTOMS: ITCH, HIVES, ANGIOEDEMA

CSU, chronic spontaneous urticaria; CU, chronic urticaria; FcεRI, high affinity IgE receptor; IgE, immunoglobulin E; IgG, immunoglobulin G

IgE implications: How does this benefit patients with CSU?

Marcus Maurer
Allergie-Centrum-Charité of the Charité - Universitätsmedizin

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Unmet need: many patients remain symptomatic after the current treatment options¹

In many patients, currently available therapies do not result in complete symptom control²

Around half of patients on current standard-of-care treatment for CSU continue to have uncontrolled symptoms³

Quick and complete symptom control to improve patient QoL is an important treatment goal for CSU²
QGE031C2201 was a Phase 2b randomized, double-blind dose-finding study

The 120 mg single-dose (SD) arm was chosen to characterise the PK/PD. Data from this arm assesses the duration of response and correlates this with the concentration of drug in serum at the time when symptoms reappear; aPatients who remained in the follow-up period for at least 12 weeks and had active disease (UAS7 ≥ 12), could enter the extension study from Week 32 onwards.

Higher changes in UAS7 were observed with ligelizumab 72 and 240 mg vs omalizumab

The mean change in UAS7 from baseline to Week 32

- Ligelizumab 24 mg q4w (n=43)
- Ligelizumab 72 mg q4w (n=84)
- Ligelizumab 120 mg SD (n=42)
- Ligelizumab 240 mg q4w (n=85)
- Omalizumab 300 mg q4w (n=85)
- Placebo (n=43)

BL, baseline; n, number of patients; UAS7, weekly Urticaria Activity Score.

More patients treated with ligelizumab achieved complete hive and urticaria activity control

*The proportion of patients achieving UAS7=0 at Week 12 was a key secondary endpoint of the core study q4w, every 4 weeks; HSS7, weekly Hives Severity Score; UAS7, weekly Urticaria Activity Score.

Benefits extended further than urticaria, showing sustained improvement in DLQI
In patients with moderate CSU activity, complete response was achieved by a numerically higher percentage of patients with ligelizumab vs omalizumab†

- At Week 4, 35.0% and 25.9% of patients achieved UAS7=0 with ligelizumab 72 and 240 mg, respectively, vs. 12.5% with omalizumab 300 mg

- At Week 12, 60.0% and 40.7% of patients achieved UAS7=0 with ligelizumab 72 and 240 mg, respectively, vs. 34.4% with omalizumab 300 mg

†Response to ligelizumab (72 and 240 mg) and omalizumab 300 mg at Week 4 and Week 12 was analysed in each group of patients separately

The percentages do not add up to 100% since some subjects discontinued the study early or due to missing data at the visit

BL, baseline; CSU, chronic spontaneous urticaria; N, number of patients; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score
In patients with severe CSU activity, complete response was achieved by a numerically higher percentage of patients with ligelizumab vs omalizumab†

- At Week 4, 28.6% and 32.1% of patients achieved UAS7=0 with ligelizumab 72 and 240 mg, respectively, vs. 22.0% with omalizumab 300 mg

- At Week 12, 38.1% and 41.1% of patients achieved UAS7=0 with ligelizumab 72 and 240 mg, respectively, vs. 20.0% with omalizumab 300 mg

†Response to ligelizumab (72 and 240 mg) and omalizumab 300 mg at Week 4 and Week 12 was analysed in each group of patients separately

*The percentages do not add up to 100% since some subjects discontinued the study early or due to missing data at the visit

BL, baseline; CSU, chronic spontaneous urticaria; N, number of patients; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score

Bernstein JA et al. European Academy of Allergy and Clinical Immunology, June 6–8, 2020, Digital congress.
Patients with active disease after the core study could enter an extension study.

<table>
<thead>
<tr>
<th>Core Study</th>
<th>Extension Study</th>
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<tbody>
<tr>
<td>Screening</td>
<td>Treatment</td>
</tr>
<tr>
<td>Wk -2</td>
<td>Wk 0</td>
</tr>
<tr>
<td>Treatment</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Wk 12</td>
<td>Wk 52</td>
</tr>
<tr>
<td>Wk 20</td>
<td>Wk 100</td>
</tr>
<tr>
<td>Wk 32</td>
<td>End of Study</td>
</tr>
<tr>
<td>Wk 44</td>
<td></td>
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</tbody>
</table>

- **Ligelizumab 240 mg q4w (n=85)**
- **Ligelizumab 72 mg q4w (n=84)**
- **Ligelizumab 24 mg q4w (n=43)**
- **Omalizumab 300 mg q4w (n=85)**
- **Ligelizumab 120 mg SD (n=42)**
- **Placebo q4w (n=42)**
- **Placebo (n=43)**

- **R** = Randomization
- **Wk 12** = Primary endpoint
- **=** Treatment visit in the core study

Ligelizumab achieved sustained symptom control

% of patients who achieved UAS7=0 up to 1 year

% of patients who achieved UAS7≤6 up to 1 year

UAS7, weekly Urticaria Activity Score.
Ligelizumab 240 mg achieved angioedema control up to 1 year

% of patients who reported angioedema up to 1 year

- 93.0% of patients were angioedema free by Week 52

Change from baseline in AAS7*¹ Scores

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Change from baseline¹</th>
<th>% change from baseline²</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 Week 4</td>
<td>82</td>
<td>-23.2 (23.7)</td>
<td>-71.9 (69.5)</td>
</tr>
<tr>
<td>E1 Week 12</td>
<td>81</td>
<td>-23.5 (25.3)</td>
<td>-68.1 (103.6)</td>
</tr>
<tr>
<td>E1 Week 20</td>
<td>75</td>
<td>-25.5 (23.8)</td>
<td>-85.5 (41.2)</td>
</tr>
<tr>
<td>E1 Week 24</td>
<td>74</td>
<td>-27.3 (25.7)</td>
<td>-84.6 (59.7)</td>
</tr>
<tr>
<td>E1 Week 52</td>
<td>69</td>
<td>-27.4 (24.6)</td>
<td>-86.3 (35.4)</td>
</tr>
</tbody>
</table>

* Angioedema Activity Score measured over 7 days on a scale ranging 0–105.
¹ Only patients with angioedema at baseline were included
² For each post-baseline week only patients with a value at both baseline and the respective week were included.

AAS7, weekly Angioedema Activity Score; E1, extension study; SD, standard deviation.
Post treatment, ligelizumab 240 mg achieved longer complete control versus other groups.

- Ligelizumab 24 mg q4w
- Ligelizumab 72 mg q4w
- Ligelizumab 240 mg q4w
- Omalizumab 300 mg q4w
- Placebo

**Proportion of patients with loss of UAS7=0 in the core study**

- Median: 3 weeks (n=8)
- Median: 4 weeks (n=33)
- Median: 10.5 weeks (n=34)

**Proportion of patients with loss of UAS7=0 in the extension study**

- Median: 11 weeks (n=120)

X represents all the censored patients who left the study without a loss of response observed; n, number of patients; q4w, every 4 weeks; UAS7, weekly Urticaria Activity Score.

More than 40% complete response with ligelizumab 240 mg in patients who had previously received omalizumab 300 mg

Patients presented were on 300 mg omalizumab in the Phase 2b core study. All patients received ligelizumab 240 mg q4w in the extension study.

Maurer M et al. European Academy of Allergy and Clinical Immunology, June 6–8, 2020, Digital congress.
Maurer M et al. European Academy of Dermatology and Venereology, October 29–31 2020, Virtual Congress.
All ligelizumab doses were well tolerated with a safety profile similar to omalizumab

<table>
<thead>
<tr>
<th>Category</th>
<th>Ligelizumab q4w</th>
<th>Omalizumab 300 mg q4w (n=85)</th>
<th>Placebo (n=43)</th>
<th>Ligelizumab 120 mg SD (n=42)</th>
<th>Total (N=382)</th>
<th>Ligelizumab 240 mg q4w (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 mg (n=43)</td>
<td>72 mg (n=84)</td>
<td>240 mg (n=85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one AE</td>
<td>36 (83.7)</td>
<td>63 (75.0)</td>
<td>63 (74.1)</td>
<td>34 (79.1)</td>
<td>37 (88.1)</td>
<td>295 (77.2)</td>
</tr>
<tr>
<td>Mild</td>
<td>16 (37.2)</td>
<td>31 (36.9)</td>
<td>32 (37.6)</td>
<td>15 (34.9)</td>
<td>22 (52.4)</td>
<td>152 (39.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>16 (37.2)</td>
<td>27 (32.1)</td>
<td>28 (32.9)</td>
<td>21 (24.7)</td>
<td>12 (27.9)</td>
<td>117 (30.6)</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (9.3)</td>
<td>5 (6.0)</td>
<td>3 (3.5)</td>
<td>5 (5.9)</td>
<td>7 (16.3)</td>
<td>26 (6.8)</td>
</tr>
<tr>
<td>At least one serious AE</td>
<td>3 (7.0)</td>
<td>2 (2.4)</td>
<td>2 (2.4)</td>
<td>3 (3.5)</td>
<td>4 (9.3)</td>
<td>18 (4.7)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
<td>2 (4.7)</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>≥1 AE possibly related to treatment</td>
<td>5 (11.6)</td>
<td>18 (21.4)</td>
<td>24 (28.2)</td>
<td>7 (8.2)</td>
<td>12 (27.9)</td>
<td>72 (18.8)</td>
</tr>
</tbody>
</table>

AE, Adverse event; SD, Single dose; q4w, every 4 weeks. Data presented as n (%). Sussman G, et al. European Academy of Allergy and Clinical Immunology in Lisbon, Portugal, June 1–5, 2019. Abstract #1178.
Management of CSU in clinical practice

Disease activity and QoL should be assessed in every stage to assess treatment response

- Omalizumab efficacy and safety in CSU is well-established
- Omalizumab is considered a third-line treatment option in the European guidelines
- Clinical trials with ligelizumab are ongoing and results may impact the CSU guidance algorithms
- Ligelizumab is currently under investigation as treatment for CSU (not approved)
## Ligelizumab Phase 3 Clinical Program

<table>
<thead>
<tr>
<th>Clinicaltrials.gov ID</th>
<th>Study ID</th>
<th>Study Description</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>NCT03580369</td>
<td>CQGE031C2302 (PEARL1)</td>
<td>A multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study to investigate the efficacy and safety of ligelizumab in the treatment of CSU in adolescents and adults inadequately controlled with H1-antihistamines</td>
<td>Active</td>
</tr>
<tr>
<td>NCT03580356</td>
<td>CQGE031C2303 (PEARL 2)</td>
<td>A multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study to establish the efficacy and safety of ligelizumab in the treatment of CSU in adolescents and adults inadequately controlled with H1-antihistamine</td>
<td>Active</td>
</tr>
<tr>
<td>NCT04210843</td>
<td>CQGE031C2302E1</td>
<td>A multicenter, double-blinded and open-label extension study to evaluate the efficacy and safety of ligelizumab as retreatment, self-administered therapy and monotherapy in CSU patients who completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301</td>
<td>Active</td>
</tr>
</tbody>
</table>

CSU, chronic, spontaneous urticaria; SC, subcutaneous. www.clinicaltrials.gov
Conclusions

Omalizumab is an effective option for the treatment of asthma and CSU

Compared with omalizumab in CSU, ligelizumab:
• Is more effective at inhibiting the IgE/FcεRI pathway
• Has a higher affinity to IgE
• Results in deeper suppression of IgE
• Has a similar safety profile and is well-tolerated

Ligelizumab benefits extend further than urticaria symptoms and can improve patients’ QoL as early as Week 4 of treatment

Ligelizumab is currently undergoing further investigation in a Phase III programme

CSU, chronic, spontaneous urticaria; DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E; QoL, quality of life.
Q&A – Redefining patient care in chronic spontaneous urticaria