

## LETTER TO THE EDITOR

### **When UAS7 = 0 is not complete: phenotype-explicit response terminology in chronic spontaneous urticaria**

*UAS7 = 0 and angioedema visibility*

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### **KEY WORDS**

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To the Editor,

the term "complete response" should not extend beyond the construct measured by the instrument used to support it. In chronic spontaneous urticaria (CSU), a weekly Urticaria Activity Score (UAS7) of 0 is commonly described as complete response or complete disease control. This is a stringent and clinically meaningful target: UAS7=0 denotes seven days without recorded wheals or itch and is associated with substantially less impairment in quality of life, sleep, activity, and work.<sup>1</sup> Importantly, the analysis supporting these associations evaluated dermatology-related quality of life, sleep, activity, and work impairment, but not an angioedema-specific activity or control measure.<sup>1</sup> The UAS7 itself contains only daily wheal-count and itch-severity items.<sup>2,3</sup> Angioedema is not scored. Consequently, UAS7=0

establishes complete wheal-and-itch response, but it cannot by itself establish the absence or control of angioedema. This distinction is illustrated in Figure 1.

This distinction matters because CSU is defined by recurrent wheals, angioedema, or both. The 2026 international urticaria guideline now makes the measurement logic explicit: patients with CSU who experience wheals and angioedema should be assessed with the UAS7 and Angioedema Activity Score (AAS) in combination; disease control should be assessed with both the Urticaria Control Test (UCT) and Angioedema Control Test (AECT).<sup>4</sup> The recommendation does not diminish the value of UAS7=0. It clarifies what that result can, and cannot, support.

Recent evidence shows why terminology has become more urgent than a theoretical measurement concern. A 2026 systematic review of 13 phase II/III randomized trials of omalizumab, dupilumab, and remibrutinib found that baseline AAS7 was reported in eight trials (61.5%), whereas AAS7 at week 24 and the Angioedema Quality of Life Questionnaire (AE-QoL) were each reported in only one trial (7.7%). Angioedema-free days were reported in three trials (23.1%).<sup>5</sup> These findings do not indicate that advanced therapies fail to improve angioedema. Rather, they show that the available reporting often cannot substantiate a phenotype-complete response claim.

The relevant instruments are complementary, not interchangeable. The AAS is a prospective daily measure of angioedema activity and can be summarized over the same seven-day window as UAS7.<sup>6</sup> The AECT retrospectively assesses angioedema control over four weeks or three months,<sup>7,8</sup> while the AE-QoL assesses angioedema-related quality-of-life impairment.<sup>9</sup> AECT should therefore be included in contemporary studies when angioedema-specific control is the construct of interest, but it is not a substitute for an aligned activity endpoint. Likewise, AE-QoL improvement does not prove the absence of attacks. The issue is

not that every historical trial should have used an instrument developed later; it is that present-day claims should be named according to the domains and time windows actually measured.

Table I proposes a phenotype-explicit lexicon. UAS7=0 should be reported as "complete wheal-and-itch response." For participants with documented angioedema during a prespecified baseline or run-in period, UAS7=0 and AAS7=0 should be presented separately at aligned time points. When both are achieved, "phenotype-complete symptom response" may be used as a transparent descriptive statement, provided that it is not presented as a newly validated composite score. Adding UAS7 and AAS7 numerically would obscure rather than solve the problem, because the instruments measure different symptom domains and have different score structures.

The denominator also requires care. Angioedema is intermittent, and AAS7=0 during a single week may occur despite clinically relevant disease over a longer interval. Analyses should therefore be restricted or stratified by recent angioedema at baseline, report the exact observation window, and complement week-level activity with longitudinal AECT and AE-QoL assessments where feasible. This approach distinguishes three questions that are frequently conflated: Were wheals and itch absent this week? Was angioedema absent this week? Was the disease controlled over a clinically meaningful longer period?

Implementation need not make trials substantially more burdensome. Protocols can: (i) document wheal and angioedema phenotypes at baseline; (ii) prespecify at least one angioedema activity outcome for participants with recent angioedema; (iii) align key UAS7 and AAS7 time points; and (iv) reserve claims of control or quality-of-life normalization for the instruments that measure those constructs. X-ACT showed that angioedema-specific burden, recurrence, and quality-of-life outcomes can be incorporated into a phase III CSU trial and can yield clinically interpretable treatment effects.<sup>10,11</sup>

The clinical scenario raised by perfect control on both UAS7 and UCT deserves separate qualification. Unlike UAS7, the UCT is not blind to angioedema: its physical-symptom item includes itch, hives, and/or swelling, and a score of 16 indicates complete disease control over the preceding four weeks.<sup>4,12</sup> By construct, concurrent UAS7=0 and UCT=16 should make clinically meaningful ongoing angioedema unlikely and constitutes a materially stronger completeness claim than UAS7=0 alone. However, UCT is a global control instrument and does not isolate the number, timing, duration, or severity of swelling episodes. The exact proportion of patients with baseline wheals and angioedema who have residual angioedema despite concurrent UAS7=0 and UCT=16 has not, to our knowledge, been quantified in a study reporting aligned UAS7, UCT, and angioedema-specific outcomes. The closest published evidence is an exploratory pooled analysis of a ligelizumab phase 2b programme: among participants with baseline angioedema, model-estimated least-squares mean AAS7 values were low but above zero when UAS7=0 (0.4 in the core study and 1.7 in the extension study); patient-level rates of UAS7=0 with AAS7>0 and concurrent UCT status were not reported.<sup>13</sup> These data suggest that wheal/itch and angioedema responses usually converge, but they do not quantify discordance after combined UAS7 and UCT complete control. The guideline similarly highlights the added value of UAS/AAS diaries when UCT indicates well-controlled but not completely controlled disease (UCT 12–15), because short-term exacerbations may otherwise be missed.<sup>4</sup>

Precision in endpoint language is not semantic pedantry. It prevents one CSU phenotype from becoming invisible, improves comparability across therapeutic programmes, and makes evidence synthesis more reliable. The risk of overclaiming is greatest when UAS7=0 is used alone or paired only with a UCT score in the well-controlled range (12–15), rather than UCT=16. Simultaneous UAS7=0 and UCT=16 provides strong evidence of overall complete control across their respective observation windows; nevertheless, phenotype-explicit

AAS7/AECT reporting remains valuable because it shows whether angioedema itself was directly measured and permits attack-specific treatment effects to be compared. UAS7=0 should remain a central target, but it should be described as complete for what it measures: wheals and itch. For patients whose CSU also includes angioedema, completeness requires that the angioedema phenotype is visible in both measurement and language.

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**Table I.** Phenotype-explicit interpretation and terminology for CSU outcome measures

| Measure                       | Construct and observation window                                                                                                          | Defensible claim                                                       | Claim not supported by this measure alone                                                 |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| UAS7=0                        | Wheal count and itch severity; prospective 7-day activity                                                                                 | Complete wheal-and-itch response                                       | Complete CSU response, angioedema response, or sustained disease control                  |
| AAS7=0                        | Angioedema activity; prospective 7-day activity                                                                                           | No angioedema activity during the aligned 7-day window                 | Sustained angioedema control beyond that window                                           |
| UCT                           | Overall urticaria control; retrospective 4-week recall, including a global physical-symptom item that covers itch, hives, and/or swelling | UCT=16: complete urticaria control; UCT 12–15: well-controlled disease | Angioedema attack frequency, duration, severity, or AAS7=0 during a specific aligned week |
| AECT                          | Angioedema-specific control; retrospective 4-week or 3-month recall                                                                       | Controlled angioedema according to the validated version and cutoff    | Attack-free status during a specific aligned 7-day window                                 |
| CU-Q2oL/AE-QoL                | Disease-specific quality-of-life impact; instrument-specific recall                                                                       | No or minimal quality-of-life impairment according to the instrument   | Absence of wheals, itch, or angioedema activity                                           |
| Co-reported UAS7=0 and AAS7=0 | Two separate, aligned activity measures in participants with documented recent angioedema                                                 | Phenotype-complete symptom response (descriptive)                      | A validated composite score or sustained remission                                        |

**Abbreviations:** AAS7, Angioedema Activity Score over 7 days; AECT, Angioedema Control Test; AE-QoL, Angioedema Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test.

**Figure 1.** UAS7=0 confirms the absence of recorded wheals and itch during a 7-day window but does not directly measure angioedema; phenotype-complete response requires explicit angioedema assessment.

