

RESEARCH LETTER

Head-to-head comparison of 4 hyaluronic acid dermal fillers for lip augmentation: A multicenter randomized, quadruple-blind, controlled clinical trial

To the Editor: Currently, no superiority of hyaluronic acid filler products over others has been shown.^{1,2} Trials have been plagued by poor methodological quality, conflicts of interest, and industry sponsoring.² Our trial assesses whether superiority in effect durability, improvement of appearance appraisal, quality of life, and safety can be shown among the 4 most frequently used hyaluronic acid dermal filler brands in the Netherlands.

We performed a multicenter, randomized, controlled, parallel, quadruple-blind clinical trial of 143 adult women who requested lip augmentation (NCT04362891). Participants (Supplementary Tables I and II, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>) were randomized (physician and product stratified) in a 1:1:1:1 ratio to receive 1.2 mL of either of the 4 hyaluronic acid dermal filler brands: Juvéderm Ultra 3, Belotero Intense, Restylane Kysse, or Stylage M (Fig 1; Supplementary Table III, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>). Between July 2021 and January 2022, they were injected by 5 board-certified cosmetic physicians at 5 locations of Faceland Clinics in the Netherlands. We used a unique blinding method in which hyaluronic acid products were transferred into blinded study syringes in a sterile operating theater (Supplementary Fig 1, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>).³ Outcomes were evaluated at baseline, day 14 (ie, “check-up”), and week 13 (ie, “follow-up”) (Supplementary Fig 2, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>).

As a result (Fig 2; Supplementary Table IV, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>), the linear mixed model analysis findings showed an overall increase in lip height (Supplementary Figs 3 and 4, available via Mendeley at <https://data.mendeley.com/datasets/gpxrsnf7pb>) from baseline to follow-up (+2.1 mm [+18.9%], $P < .01$); with Stylage (+2.8 mm [+26.3%]), lip height increased more than with Juvéderm (+1.2 mm

[+10.9%], $d = 0.73$). Overall, appearance appraisal increased from baseline to follow-up (+9.4 points on a 10–40 point scale [+40.7%], $P < .01$), and increased more with Juvéderm (+10.9 points [+50.7%]) than with Belotero (+7.2 points [+29.8%], $d = 0.50$). No serious adverse events were recorded.⁴ Overall, social function (+2.4 points on a 8–32 point scale [+9.8%], $P < .01$) and psychological well-being (+2.7 points on a 10–40 point scale [+8.7%], $P < .01$) scores increased from baseline to follow-up. Social function increased more with Stylage (+4.6 points [+20.1%]) than with Belotero (+1.6 points [+6.3%]; $d = 0.64$). Overall, lip height increased from baseline to check-up (+3.8 mm [+34.4%], $P < .01$). Belotero (+4.7 mm [+41.3%]) resulted in a greater increase than both Juvéderm (+3.1 mm [+27.7%], $d = 1.21$) and Stylage (+3.4 mm [+31.1%], $d = 0.58$). Juvéderm was associated with higher side effect scores (13.0 points on a 8–32 point scale) 25.3% than Stylage (12.0 points; $d = 0.85$).

Not all statistically significant differences between the products observed may be clinically relevant. A successful lip filler treatment is the result of the combination of a visually volumizing effect, satisfaction with anatomical shape, function, recovery, and psychosocial effects. At follow-up, no between-group difference was found for any of these outcomes. We showed that side-effect profiles were low, and, at month 3, lip appraisal, treatment satisfaction, and quality of life were high in all groups. Nonetheless, the absolute difference in lip volume increase from baseline to follow-up between Juvéderm versus Stylage was 1.6 mm (15.4%) in this sample of women with relatively small lips (an average of 10.9 mm at baseline), suggesting a clinically relevant longer duration of Stylage. Last, the absolute difference in the lip appraisal score increase between Juvéderm versus Belotero was 20.9%, suggesting a clinically relevant better appraisal of Juvéderm over time.

In conclusion, statistically significant but clinically arguably relevant superiority was found in duration, patient satisfaction, and quality of life. No product was superior in all categories. Safety profiles were equal. Future dermal filler trials would benefit from the use of stereophotogrammetry for accurate volume quantification.⁵

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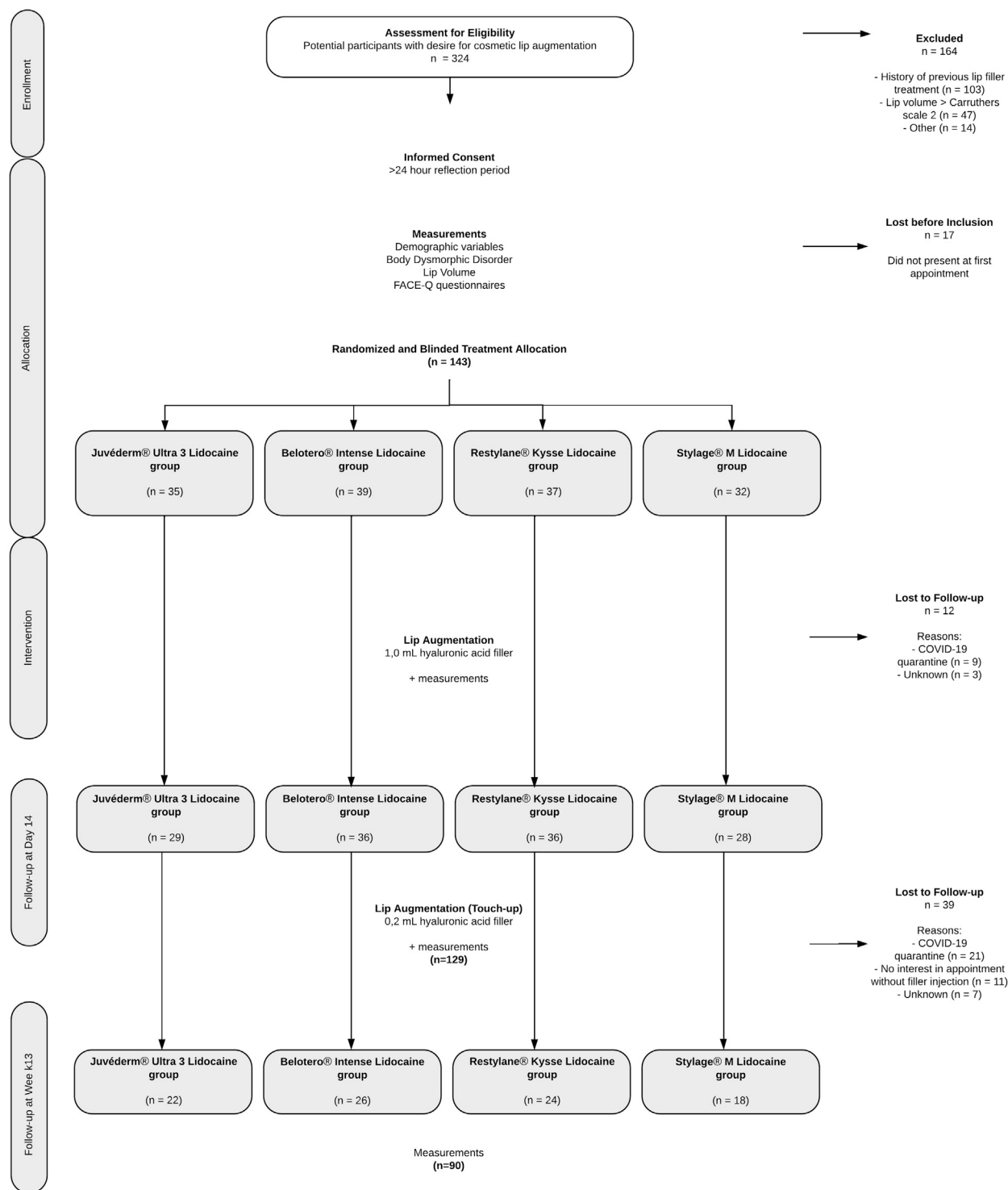


Fig 1. Participant flow diagram and study procedures in a randomized trial investigating a head-to-head comparison of 4 hyaluronic acid dermal fillers.

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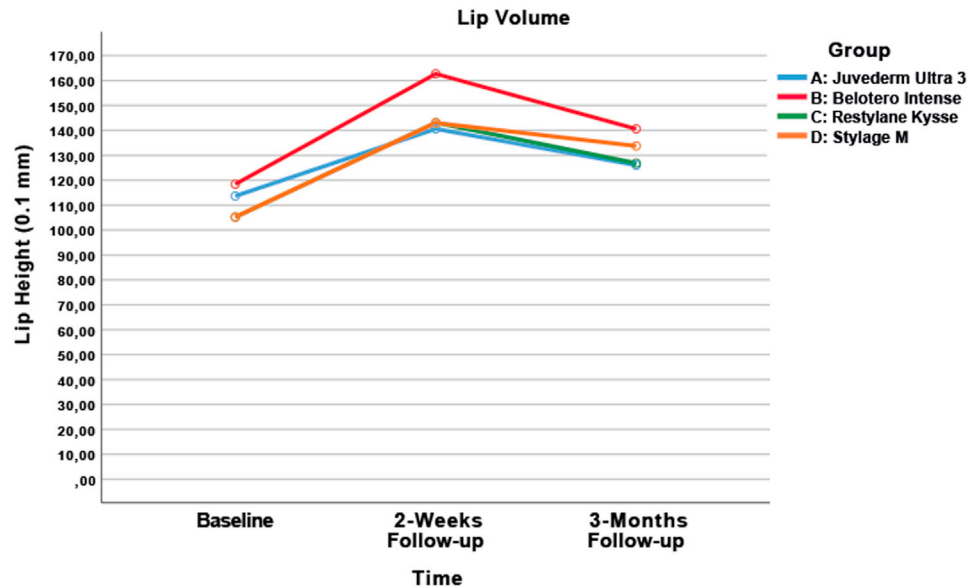


Fig 2. Observed trajectories of the primary outcome as a function of the treatment group in a randomized trial investigating a head-to-head comparison of 4 hyaluronic acid dermal fillers.

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Key words: adverse events; Belotero; cosmetic techniques; dermal fillers; esthetics; FACE-Q; hyaluronic acid; injections; Juvéderm; lip; quality of life; randomized controlled trial; Restylane; self-assessment; Stylage; treatment outcome.

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Conflicts of interest

None disclosed.

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