We thank Dr Masood for his interest in our work[1] and for giving us the chance to discuss some crucial aspects of our analysis.

His first comment pertains to the small difference in medicated intraocular pressure (IOP) between the two arms and the fact that its effect only explained a small proportion of the observed difference on the average rate of visual field progression. From our paper, Dr Masood concluded that our explanation for this effect was a modification of the aqueous dynamics and a dampening of IOP fluctuations by the Hydrus microstent. However, this is not what we intended to imply, and we apologize for his confusion. When referring to a protective effect of a more regular IOP profile with the Hydrus, we were not speculating on the effect of fluctuations *per se* on visual field progression (i.e. the variability of pressure control), but rather on the fact that patients receiving the Hydrus microstent might have been less likely to suffer from a higher IOP outside office-hours, when not monitored, because of the continuous action of the stent. Dr Masood correctly refers to some secondary results of the analysis of UKGTS visual field data[2], showing no effect of IOP fluctuations on glaucoma progression. Two of the authors of the paper being discussed (DPC and GM) were also involved in that work. In that analysis, IOP fluctuations were used as predictors of change after factoring out the effect of the average IOP, i.e. the fluctuations were 'normalised' to eliminate the concomitant effect of higher IOP associated with them. However, fluctuations can also determine a higher average IOP, and we hypothesised that this was the main reason behind the residual unexplained effect on visual field progression. This is, however, speculation and does not detract from the validity of the significant effect observed by comparing the two randomised arms of the trial.

Dr Masood is also perplexed by the fact that the average IOP was very similar between the two groups. It should be pointed out, however, that this average IOP excluded the washed out IOP measurements at 12 and 24 months. These did indeed show a much larger difference between the two arms, in agreement with the expected additional effect of the MIGS procedure[3]. In the trial, clinicians escalated treatment as needed to achieve optimal IOP control[3-5] and therefore, large differences in medicated IOP would have been, in fact, surprising. This is similar to the LiGHT trial, where a rigorous protocol was set up to achieve the target IOP between the two arms[6]. Yet, in both LiGHT[7] and HORIZON[1], we observed significantly faster visual field progression in the arms where patients did not benefit from a more continuous method to control their IOP. In the HORIZON trial, this was despite the fact that the cataract surgery alone arm was more heavily medicated and agrees with the observation that patients in this arm underwent incisional glaucoma surgery more frequently that patients receiving Hydrus[4, 5]. It is important to note that, while poor compliance with medications might contribute to suboptimal IOP control, drops do not have, by their nature, a continuous action on IOP even in compliant patients, and this might also play a role.

Dr Masood also refers to two landmark trials (CIGTS and TAGS) comparing surgical and medical interventions, which failed to show a significant difference on visual field progression. This is an important point that needs to be addressed for the two trials separately. In CIGTS, the visual field outcomes were analysed in a few different ways. The main outcome was based on a survival analysis of the time to detect a progression "event"[8]. Event-based progression for trials has been shown to be much less powerful than trend

based progression[9, 10]. Indeed, a big effort in the literature is being devoted to validating trend based analyses for neuroprotection trials[11, 12], which would be essentially impossible with event-based methodology. A later analysis in CIGTS, however, did explore the change of mean deviation (MD) over time using linear mixed models, similarly to us. This analysis also failed to show a significant difference between the two arms in unadjusted analyses[13]. Interestingly, an additional analysis found a significant effect of parameters IOP control on the rate of visual field decline in the medicine-first arm, but not in the surgery first arm, supporting our hypothesis[14]. That said, it might be helpful, and reassuring, to report that *we also found no difference in the HORIZON trial when analysing the trend of the MD and mean sensitivity*. Indeed, a significant difference only emerged when analysing pointwise sensitivity data with linear mixed models (the pre-specified main outcome analysis). This speaks to the issue of the sensitivity of the method chosen for the analysis in determining the significance of the results. **Table 1** reports these additional analyses compared to the main outcome. The most likely explanation for this discrepancy is that granular pointwise data allowed a more precise characterisation of the fast progressing patients in the cataract only arm, which was the main factor influencing the average difference in rate. This result is somewhat reminiscent to what we reported for LiGHT, where significant differences were only apparent when analysing pointwise data[7]. Please note that that these are the secondary results obtained with an off-the-shelf package to fit linear mixed models in R, and therefore easily replicable on any dataset, but our main results in the paper used a more sophisticated Bayesian method for estimation.

| | | CS-HMS | CS | Difference | p |
|---|---|---|---|---|---|
| **Pointwise sensitivity** | **Baseline (dB)** | 26.62 [26.32, 26.93] | 26.62 [26.17, 27.06] | 0.00 [-0.54, 0.53] | 0.989 |
| | **RoP (dB/year)** | -0.26 [-0.36, -0.17] | -0.47 [-0.61, -0.33] | -0.21 [-0.37, -0.04] | **0.0149** |
| **Total deviation** | **Baseline (dB)** | -2.68 [-2.98, -2.38] | -2.71 [-3.14, -2.27] | -0.02 [-0.55, 0.51] | 0.9296 |
| | **RoP (dB/year)** | -0.20 [-0.29, -0.11] | -0.41 [-0.54, -0.27] | -0.21 [-0.37, -0.04] | **0.0151** |
| **Mean sensitivity** | **Baseline (dB)** | 26.62 [26.32, 26.93] | 26.50 [26.06, 26.94] | -0.12 [-0.66, 0.41] | 0.6521 |
| | **RoP (dB/year)** | -0.27 [-0.34, -0.20] | -0.36 [-0.47, -0.25] | -0.09 [-0.23, 0.04] | 0.1677 |
| **Mean deviation** | **Baseline (dB)** | -2.60 [-2.89, -2.31] | -2.75 [-3.17, -2.33] | -0.15 [-0.66, 0.37] | 0.5783 |
| | **RoP (dB/year)** | -0.21 [-0.28, -0.14] | -0.30 [-0.40, -0.19] | -0.09 [-0.21, 0.04] | 0.1967 |

**Table 1.** All estimates are reported as Mean [95% Confidence]. CS = Cataract Surgery; HMS = Hydrus microstent; RoP = Rate of progression.

For TAGS, we have recently published a detailed report of the visual field outcomes[15], performing an analysis essentially identical to the one presented for HORIZON. While it is true that the main analysis in TAGS failed to reach significance, some of the secondary analyses either came very close or did reach significance. As pointed out by Dr Masood, however, the effect was expected to be much larger for trabeculectomy than a MIGS procedure. However, it should be noted that TAGS was also not designed to test differences in visual field progression. Moreover, in TAGS, patients were only followed up for two years and tested a 4 time-points, limiting the power of the analysis. Further loss of power derived from having recruited patients with advanced damage, whose perimetric tests are fraught with increased variability and are closer to the measurement floor, limiting the chances to

detect differences in progression. In contrast, the HORIZON recruited mostly moderate glaucoma patients and followed them up for 5 years. A 5-year follow-up data collection for TAGS is underway and we hope to be able to provide the results of this additional analysis soon.

Ultimately, we agree with Dr Masood that too few of the recent glaucoma trials have focused their design on comparing medium- and long-term preservation of visual field, a key factor in deciding the treatment approach for clinicians and patients alike. However, we would like to emphasize that our analysis for HORIZON was carefully designed to approximate the results of a prospective randomised clinical trial as closely as possible[1]. Importantly, the analysis was pre-specified before data extraction and conducted by the researchers blinded to the treatment assignment. This prevented a preliminary inspection of the data from influencing the choice of methodology. Moreover, the use of linear mixed models allowed the inclusion of the vast majority of patients in the final analysis (including participants with as little as two visual fields in the sensitivity analysis) to reduce the chances of selection bias and to preserve the effect of randomization. This gives us confidence in the veracity of our results.

One final point that should be emphasized, especially when comparing our results to previous literature, is that the lack of a significant difference does not prove equivalence between two treatments. More sophisticated analyses are becoming available and give us the chance to refine our metrics and improve the power of our studies. Revisiting the results of previous randomised clinical trials will be important not only to shed new light on the effect of glaucoma treatments, but also to inform the design of future research.

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