

S8: Mediation effect estimates in the presence of treatment-mediator interaction

The outcome models that included a treatment by mediator (TxM) interaction did not result in a significant improvement in model fit. The main text of the paper therefore reports the mediation results based on the assumption of no-interaction. Nevertheless, to better understand the impact of TxM interaction on mediation, we include the results in Table E.

Causal effect estimates for the 3 vision outcomes

Table E displays the causal effect estimates. The mediation effect represents the effect of ocriplasmin on vision outcomes through ocriplasmin's treatment effect on VMAR. In OASIS, the *mediated effect under treatment condition IE(1)* represents the average treatment effect on the vision outcome that is transmitted by the change in VMAR induced by ocriplasmin. The IE(1) answers the counterfactual question: What change would occur to the probability of the vision outcome if the level of VMAR changed from what would be realized under sham $M(0)$, to the level of VMAR that would be observed under ocriplasmin $M(1)$, while holding the treatment constant at ocriplasmin ($t=1$). More specifically, the mediated effect is a comparison of the probability of a vision improvement when the level of VMAR were those that what would occur with ocriplasmin vs the probability of a vision improvement when the level of VMAR were those that would occur with sham but in fact occurred during receipt of ocriplasmin therapy. The *direct effect under control condition DE(0)* compares the effect of ocriplasmin ($t=1$) vs. sham ($t=0$) on vision outcomes while holding the level of VMAR constant at the level that would be realized under sham treatment $M(0)$. The total treatment effect is broken down into the *mediated effect IE(1)* and *direct effect DE(0)*. Total treatment effect represents how much (%) the vision outcomes would change overall, for a change in the exposure from sham to ocriplasmin.

Table A: Causal effect estimates for the binary vision outcomes – impact treatment by mediator interaction

Average effects (%)	No T by M interaction	With T by M interaction
VFQ-I[†]		
IE (1)[†] [95% CI]	5.7 [‡] [1.16 , 10.86]	7.8 [-4.29 , 19.22]
DE (0)[†] [95% CI]	8.3 [-3.30 , 19.53]	8.1 [-3.90 , 18.57]
TTE[†] [95% CI]	13.9 [‡] [2.61 , 24.23]	15.9 [-3.39 , 31.58]
% TTE mediated via IE (1)	40.0 [22.75 , 167.28]	44.3 [-215.90 , 328.88]
VA-I[†]		
IE (1)[†] [95% CI]	11.8 [‡] [4.99 , 19.41]	9.8 [-1.94 , 20.81]
DE (0)[†] [95% CI]	12.2 [‡] [1.53 , 22.95]	11.5 [-0.32 , 22.45]
TTE[†] [95% CI]	23.9 [‡] [12.15 , 34.97]	21.3 [‡] [2.28 , 36.78]
% TTE mediated via IE (1)	48.9 [33.67 , 96.77]	43.8 [25.29 , 218.17]
VF-I[†]		
IE (1)[†] [95% CI]	5.2 [-0.31 , 11.31]	2.4 [-10.00 , 15.74]
DE (0)[†] [95% CI]	24.1 [‡] [11.58 , 36.56]	22.9 [‡] [9.52 , 35.56]
TTE[†] [95% CI]	29.3 [‡] [17.81 , 40.20]	25.4 [‡] [4.46 , 42.21]
% TTE mediated via IE (1)	17.7 [12.98 , 29.28]	9.25 [5.64 , 44.03]

[†]Risk difference at month 24

[†] IE (1): indirect effect under treatment condition, ocriplasmin ($t=1$); DE (0): direct effect under control condition, sham ($t=0$); TTE: total treatment effect (difference in observed % of ocriplasmin-treated participants with a vision improvement vs. sham-treated participants).

[‡] Results with significant values at $p<0.05$.

The dynamics of mediation can be appreciated when we compare the scenario with vs. without T by M interaction. When interaction is introduced, the mediated effect under ocriplasmin condition

changes from a significant risk difference (RD) of 5.7% to a nonsignificant RD of 7.8% for VFQ-I, and from 11.8% to a nonsignificant RD of 9.8%. When adding a T by M interaction term, the causal effects for VF-I remain nonsignificant.