



Addendum for the Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea Single Technology Appraisal following a Patient Access Scheme

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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1 Background

In February 2019, the company submitted to the National Institute for Health and Care Excellence (NICE) the evidence for use of clostridium botulinum toxin A (CBTA) (Xeomin®) in the treatment of chronic sialorrhoea.¹ Following the Technical Engagement step, the company submitted a Patient Access Scheme (PAS) involving a simple discount of ██████ resulting in an acquisition price of ██████ for 100U of CBTA compared with the list price of £129.90.

2 Company's cost effectiveness analysis incorporating the PAS

2.1 Summary of evidence submitted

Following the PAS submission, the company presented new base case cost-effectiveness results based on its most recent cost-effectiveness model. Table 1 and Table 2 present the base case results without and with PAS respectively.

Within this section, the ERG reproduces these analyses incorporating the PAS.

Table 1: Company's revised model - base case results (without PAS)

| Intervention | Total costs (discounted) | Total LYG (discounted) | Total QALYs (discounted) | Incr. costs | Incr. LYG | Incr. QALYs | ICER for Xeomin versus comparator (£/QALY) |
|---------------------------------|--------------------------|------------------------|--------------------------|-------------|-----------|-------------|--|
| Xeomin plus Soc | £6,103 | 8.18 | 3.52 | | | - | |
| Glycopyrronium bromide plus SoC | £14,966 | 8.18 | 3.34 | £8,863 | 0.00 | 0.18 | Xeomin plus SoC dominant |
| SoC alone | £3,010 | 8.18 | 3.20 | £3,093 | 0.00 | 0.32 | £9,583 |

Table 2: Company's revised model - base case results (with PAS)

| Intervention | Total costs (discounted) | Total LYG | Total QALYs (discounted) | Incr. costs | Incr. LYG | Incr. QALYs | ICER for Xeomin versus comparator (£/QALY) |
|---------------------------------|--------------------------|-----------|--------------------------|-------------|-----------|-------------|--|
| Xeomin plus Soc | ████ | ██ | ██ | | | | |
| Glycopyrronium bromide plus SoC | ████ | ██ | ██ | ████ | ██ | ██ | ████████████████ ████ |
| SoC alone | ████ | ██ | ██ | ████ | ██ | ██ | ████ |

2.2 Critique of company's approach

Section 4.3.4 of the ERG report provides details of the main issues identified by the critical appraisal conducted by the ERG.² This text is not reproduced here for brevity. The ERG's exploratory analyses and base case are provided in Section 3.

3 ERG's cost effectiveness results when incorporating the PAS

The ERG replicated its base case cost effectiveness analysis and exploratory analyses detailed in Section 4.4 of the ERG report incorporating the proposed PAS.² As in Section 5 of the ERG report, all results were run deterministically with probabilistic analyses conducted only for the ERG base case. Table 3 and Table 4 presents the exploratory analyses (with PAS) undertaken by the ERG for severe and moderate patients respectively. For completeness, as the Technical Engagement document did not consider disease severity, Table 5 presents the same analyses for the entire patient population.

3.1 Interpreting the deterministic analyses incorporating the PAS

The utility values associated with the severity of sialorrhoea remained the key driver of the ICER for CBTA + standard care (SoC) compared with SoC alone. However, the PAS introduction led to observable decrease in the ICER values associated with the ERG's base case.

For patients with severe sialorrhoea the deterministic ICER of CBTA + SoC compared with SoC alone rose to over █████ (compared with over £44,000 at list price) using the utility values generated directly from the SIAXI trial and the ERG's LCMM approach. For moderate patients, this value was above █████ (compared with above £50,000 at list price) and was over █████ (compared with over £47,000 at list price) in the combined severity patient population.

The ERG's base case ICERs increase if 1) all CBTA injections were guided with ultrasound and there was no increase in effectiveness of treatment and 2) if resource use did not alter based on the severity of sialorrhoea.

CBTA dominated glycopyrronium bromide in all of the analyses undertaken by the ERG.

3.2 ERG base case probabilistic results incorporating the PAS

The ERG performed probabilistic sensitivity analyses (PSA) using 1,000 iterations. Cost-effectiveness acceptability curves and cost-effectiveness planes are presented in Appendix 1. Using the PAS price of CBTA, the ERG base case probabilistic ICER of CBTA + SoC compared with SoC was over ██████ for severe patients, over ██████ for moderate patients, and over ██████ for the overall population (compared with £41,000, £48,000 and £45,000 respectively at list price).

Compared with SoC alone and using the PAS price, the probability of CBTA + SoC being cost-effective at a cost per QALY gained threshold of £20,000 increased to ██████, ██████, and ██████ for severe, moderate and all patients respectively. At a threshold of £30,000, the respective probabilities increased to ██████, ██████, and ██████.

CBTA + SoC was cost-effective in ██████ of the PSA iterations for both severe and moderate patients compared with glycopyrronium bromide using a cost per QALY gained threshold of £20,000.

Table 3: Exploratory model results for severe patients (with PAS)

| Analysis | Discounted costs | | | Discounted QALYS | | | ICER (CBTA + SoC versus SoC) |
|---|------------------|---------------|--------|------------------|---------------|-------|------------------------------|
| | CBTA + SoC | Glyc Br + SoC | SoC | CBTA + SoC | Glyc Br + SoC | SoC | |
| Company base case | ████ | £15,020 | £3,070 | ████ | 3.318 | 3.175 | ████ |
| 1) Using the company's LCMM model | ████ | £15,020 | £3,070 | ████ | 4.914 | 4.876 | ████ |
| 2) Applying the ERG's LCMM utility values | ████ | £15,020 | £3,070 | ████ | 4.875 | 4.846 | ████ |
| 3) Correcting CBTA administration costs | ████ | £15,020 | £3,070 | ████ | 3.318 | 3.175 | ████ |
| 4) Severe patients discontinue active treatment after second treatment cycle | ████ | £10,693 | £3,070 | ████ | 3.268 | 3.175 | ████ |
| 5) Mild patients who discontinue active treatment, transition to the moderate health state [□] | ████ | £15,013 | £3,070 | ████ | 3.323 | 3.175 | ████ |
| 6) Applying the modified correction factor* | ████ | £15,108 | £3,210 | ████ | 3.287 | 3.125 | ████ |
| 7) Adjusting the population's SMR value | ████ | £13,146 | £2,544 | ████ | 2.732 | 2.610 | ████ |
| 8) Correcting the acquisition costs for glycopyrronium bromide | ████ | £14,076 | £3,070 | ████ | 3.318 | 3.175 | ████ |
| ERG base case (scenarios 2 – 8) | ████ | £9,505 | £2,661 | ████ | 4.003 | 3.982 | ████ |
| ERG base case (probabilistic results) | ████ | £9,324 | £2,469 | ████ | 3.698 | 3.675 | ████ |
| ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2) | ████ | £9,505 | £2,661 | ████ | 2.673 | 2.567 | ████ |
| 9) Assuming all patients require an ultrasound scan for the CBTA injections [†] | ████ | £9,505 | £2,661 | ████ | 4.003 | 3.982 | ████ |
| 10) Assuming no additional resource use for the different sialorrhoea severity levels [†] | ████ | £7,110 | £0 | ████ | 4.003 | 3.982 | ████ |

[□] This produces more QALYs than the base case due to the continuity correction applied in the mild health state * In conjunction with scenario 5 [†]In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

Table 4: Exploratory model results for moderate patients (with PAS)

| Analysis | Discounted costs | | | Discounted QALYS | | | ICER (CBTA + SoC versus SoC) |
|---|------------------|---------------|--------|------------------|---------------|-------|------------------------------|
| | CBTA + SoC | Glyc Br + SoC | SoC | CBTA + SoC | Glyc Br + SoC | SoC | |
| Company base case | ■ | £14,900 | £2,939 | ■ | 3.371 | 3.233 | ■ |
| 1) Using the company's LCMM model | ■ | £14,900 | £2,939 | ■ | 4.920 | 4.882 | ■ |
| 2) Applying the ERG's LCMM utility values | ■ | £14,900 | £2,939 | ■ | 4.884 | 4.856 | ■ |
| 3) Correcting CBTA administration costs | ■ | £14,900 | £2,939 | ■ | 3.371 | 3.233 | ■ |
| 4) Severe patients discontinue active treatment after second treatment cycle | ■ | £11,306 | £2,939 | ■ | 3.330 | 3.233 | ■ |
| 5) Mild patients who discontinue active treatment, transition to the moderate health state [□] | ■ | £14,893 | £2,939 | ■ | 3.376 | 3.233 | ■ |
| 6) Applying the modified correction factor* | ■ | £14,974 | £3,061 | ■ | 3.346 | 3.190 | ■ |
| 7) Adjusting the population's SMR value | ■ | £13,028 | £2,414 | ■ | 2.784 | 2.667 | ■ |
| 8) Correcting the acquisition costs for glycopyrronium bromide | ■ | £13,956 | £2,939 | ■ | 3.371 | 3.233 | ■ |
| ERG base case (scenarios 2 – 8) | ■ | £10,001 | £2,515 | ■ | 4.014 | 3.992 | ■ |
| ERG base case (probabilistic results) | ■ | £9,832 | £2,321 | ■ | 3.747 | 3.724 | ■ |
| ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2) | ■ | £10,001 | £2,515 | ■ | 2.740 | 2.632 | ■ |
| 9) Assuming all patients require an ultrasound scan for the CBTA injections [†] | ■ | £10,001 | £2,515 | ■ | 4.014 | 3.992 | ■ |
| 10) Assuming no additional resource use for the different sialorrhoea severity levels [†] | ■ | £7,759 | £0 | ■ | 4.014 | 3.992 | ■ |

[□] This produces more QALYs than the base case due to the continuity correction applied in the mild health state *In conjunction with scenario 5 [†]In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

Table 5: Exploratory model results for entire population (with PAS)

| Analysis | Discounted costs | | | Discounted QALYS | | | ICER (CBTA + SoC versus SoC) |
|---|------------------|---------------|--------|------------------|---------------|-------|------------------------------|
| | CBTA + SoC | Glyc Br + SoC | SoC | CBTA + SoC | Glyc Br + SoC | SoC | |
| Company base case | ██████ | £14,966 | £3,010 | ██████ | 3.342 | 3.202 | ██████ |
| 1) Using the company's LCMM model | ██████ | £14,966 | £3,010 | ██████ | 4.917 | 4.878 | ██████ |
| 2) Applying the ERG's LCMM utility values | ██████ | £14,966 | £3,010 | ██████ | 4.879 | 4.850 | ██████ |
| 3) Correcting CBTA administration costs | ██████ | £14,966 | £3,010 | ██████ | 3.342 | 3.202 | ██████ |
| 4) Severe patients discontinue active treatment after second treatment cycle | ██████ | £10,972 | £3,010 | ██████ | 3.296 | 3.202 | ██████ |
| 5) Mild patients who discontinue active treatment, transition to the moderate health state [□] | ██████ | £14,959 | £3,010 | ██████ | 3.347 | 3.202 | ██████ |
| 6) Applying the modified correction factor* | ██████ | £15,047 | £3,142 | ██████ | 3.314 | 3.154 | ██████ |
| 7) Adjusting the population's SMR value | ██████ | £13,092 | £2,485 | ██████ | 2.756 | 2.636 | ██████ |
| 8) Correcting the acquisition costs for glycopyrronium bromide | ██████ | £14,021 | £3,010 | ██████ | 3.342 | 3.202 | ██████ |
| ERG base case (scenarios 2 – 8) | ██████ | £9,730 | £2,594 | ██████ | 4.008 | 3.987 | ██████ |
| ERG base case (probabilistic results) | ██████ | £9,384 | £2,396 | ██████ | 3.714 | 3.691 | ██████ |
| ERG base case (using the NG utility values, i.e. excluding scenarios 1 and 2) | ██████ | £9,730 | £2,594 | ██████ | 2.703 | 2.597 | ██████ |
| 9) Assuming all patients require an ultrasound scan for the CBTA injections [†] | ██████ | £9,730 | £2,594 | ██████ | 4.008 | 3.987 | ██████ |
| 10) Assuming no additional resource use for the different sialorrhoea severity levels [†] | ██████ | £7,405 | £0 | ██████ | 4.008 | 3.987 | ██████ |

[□] This produces more QALYs than the base case due to the continuity correction applied in the mild health state * In conjunction with scenario 5 [†]In conjunction with the ERG base case

CBTA, Clostridium botulinum toxin A; Glyc Br, Glycopyrronium Bromide; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; SoC, Standard of Care

3.3 One-way deterministic sensitivity analysis incorporating the PAS

The ERG’s tornado diagrams are presented in Appendix 2 (assuming a cost per QALY gained threshold of £20,000) and Appendix 3 (assuming a cost per QALY gained threshold of £30,000). The deterministic results remain robust. The incremental net monetary benefit (NMB) associated with CBTA + SoC was higher than glycopyrronium bromide arm, whereas it was below zero (indicating an ICER above the threshold) compared with SoC alone.

3.4 Threshold analysis incorporating the PAS

A threshold analysis was undertaken to determine the utility difference between the three different health states needed to be obtain to provide a cost per QALY gained of £20,000 and £30,000.. At an ICER of £20,000 per QALY gained, the differences needed to increase by [REDACTED] times, [REDACTED] times, and [REDACTED] times for severe patients, moderate patients, and the overall population respectively. These factors were [REDACTED], [REDACTED] and [REDACTED] at an ICER of £30,000 for patients with severe, moderate, and combined severity respectively. The disutilities that these multipliers equate to are provided in Table 6 and Table 7.

Table 6: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £20,000

| | An initial population with severe sialorrhoea | An initial population with moderate sialorrhoea | An initial population with severe or moderate sialorrhoea |
|--|---|---|---|
| Disutility associated with moderate sialorrhoea [†] | [REDACTED] | [REDACTED] | [REDACTED] |
| Disutility associated with severe sialorrhoea [†] | [REDACTED] | [REDACTED] | [REDACTED] |

[†] Compared with mild / resolved sialorrhoea.

Table 7: The disutilities required with the sialorrhoea severity states in order to reach a cost per QALY gained value of £30,000

| | An initial population with severe sialorrhoea | An initial population with moderate sialorrhoea | An initial population with severe or moderate sialorrhoea |
|--|---|---|---|
| Disutility associated with moderate sialorrhoea [†] | ■ | ■ | ■ |
| Disutility associated with severe sialorrhoea [†] | ■ | ■ | ■ |

[†] Compared with mild / resolved sialorrhoea.

Appendix 1: The ERG's probabilistic results. PAS incorporated

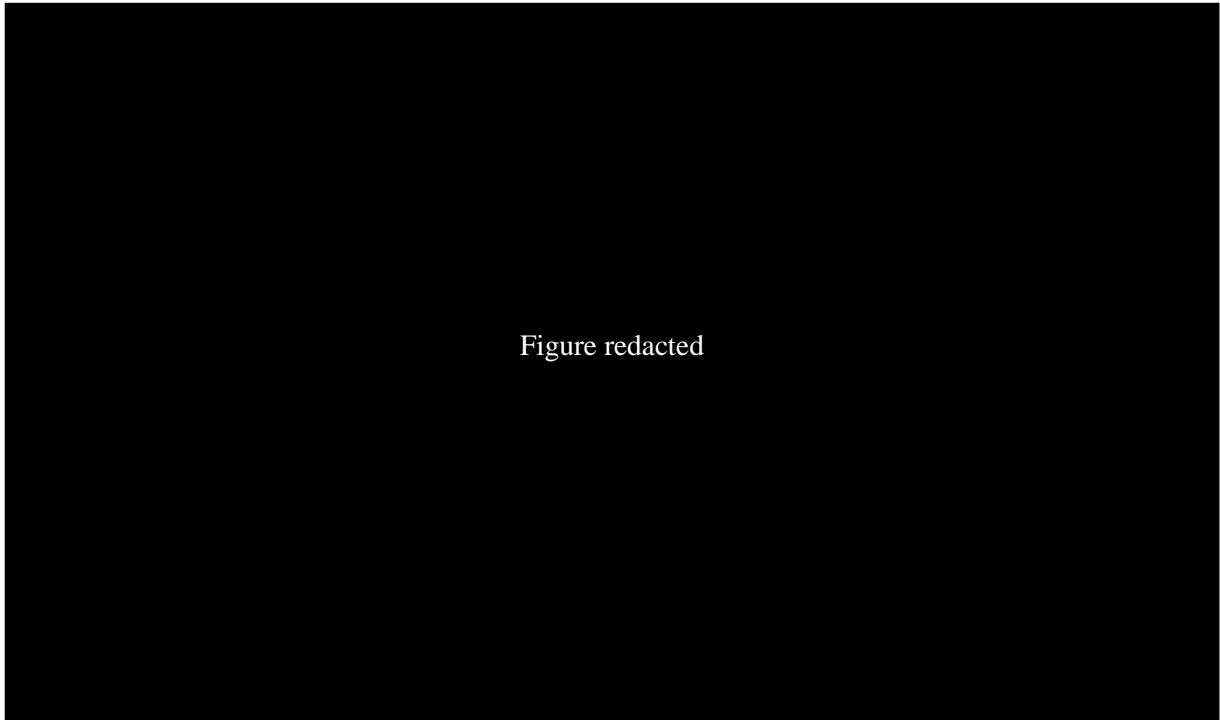


Figure 1: ERG's base case cost-effectiveness acceptability curve (severe patients)

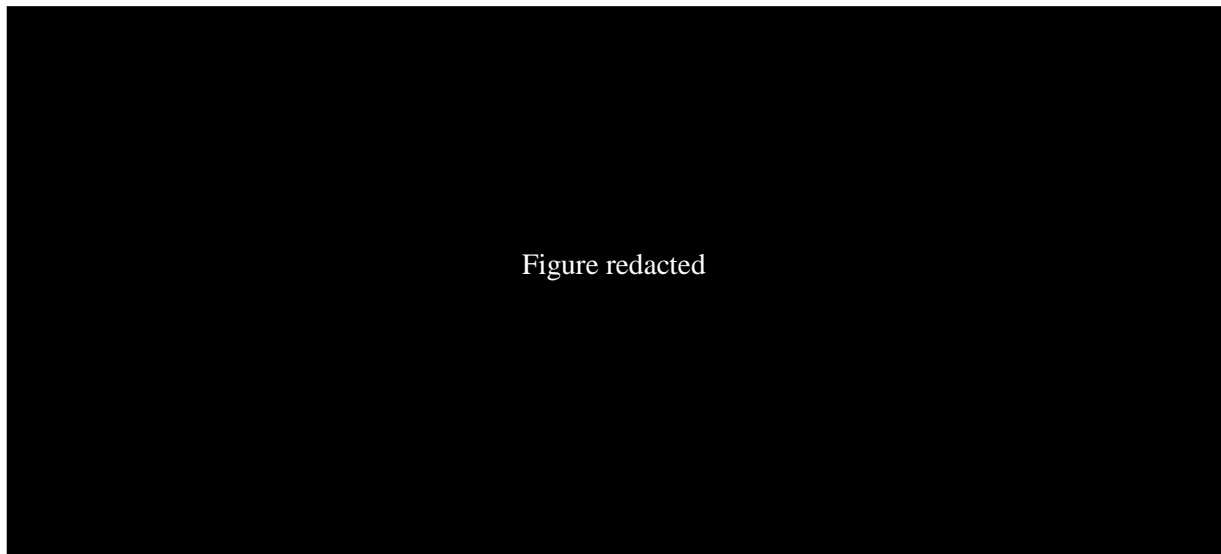


Figure 2: ERG's cost-effectiveness planes of CBTA + SoC (severe patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

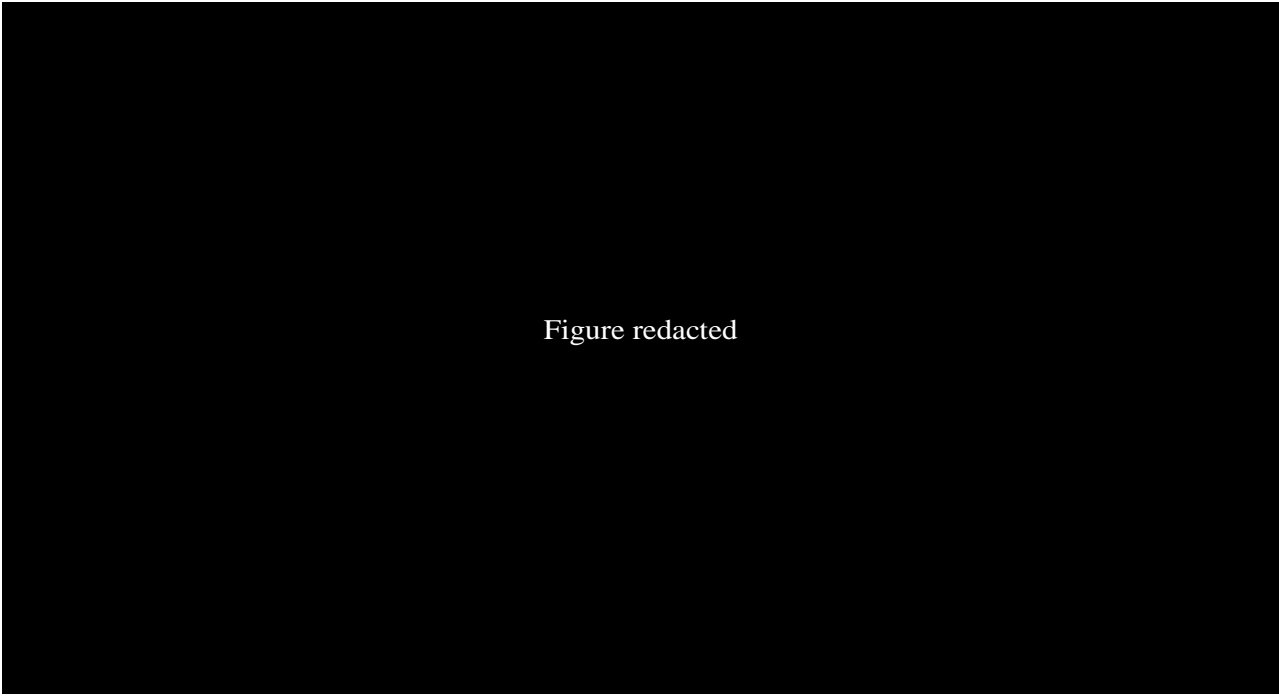


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Figure 3: ERG's base case cost-effectiveness acceptability curve (moderate patients)

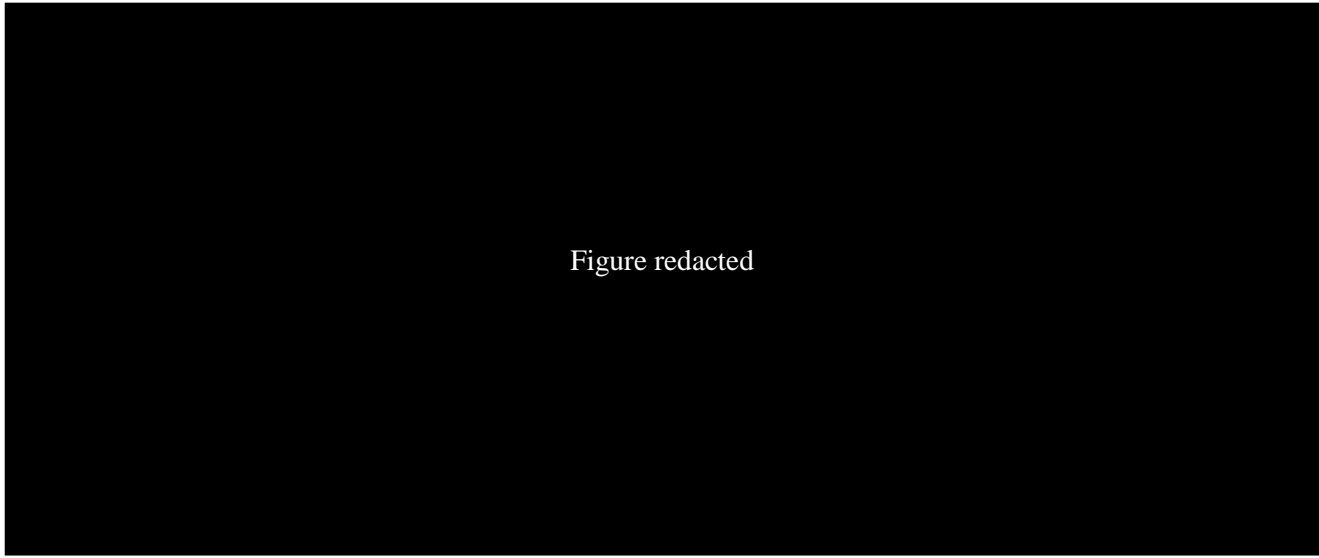


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Figure 4: ERG's cost-effectiveness planes of CBTA + SoC (moderate patients) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

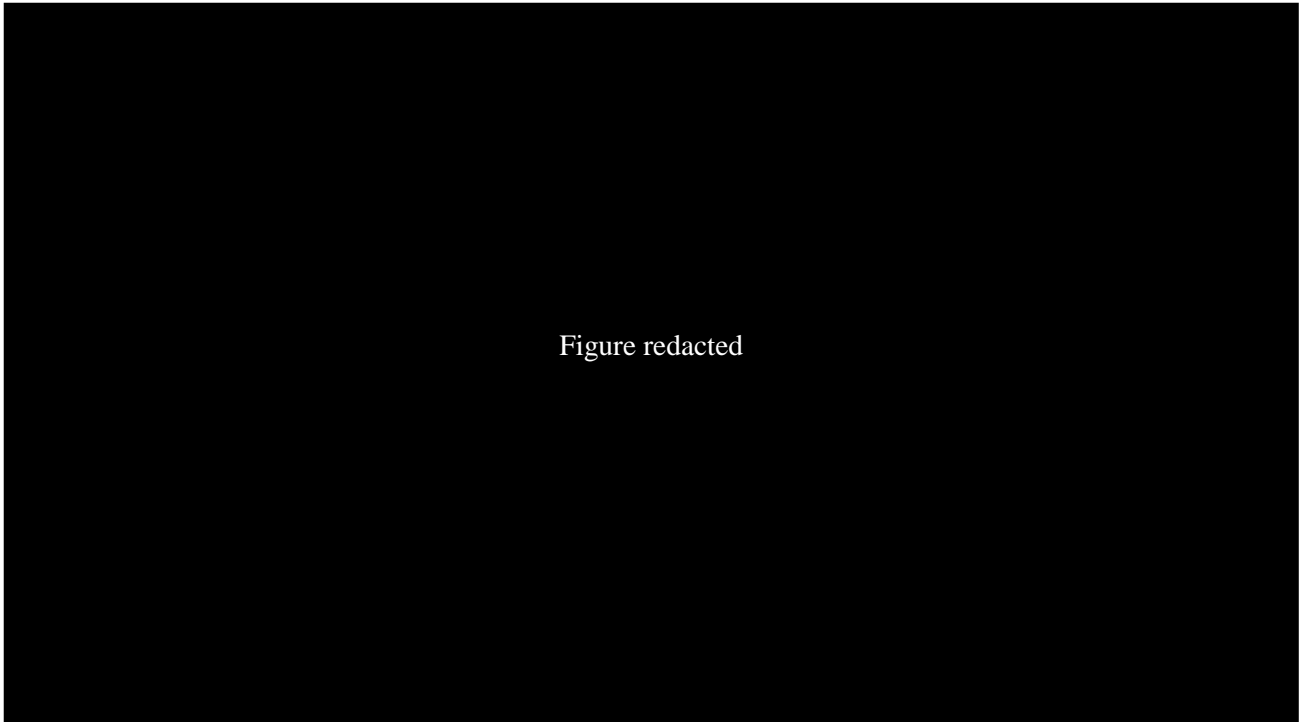


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Figure 5: ERG's base case cost–effectiveness acceptability curve (overall population)

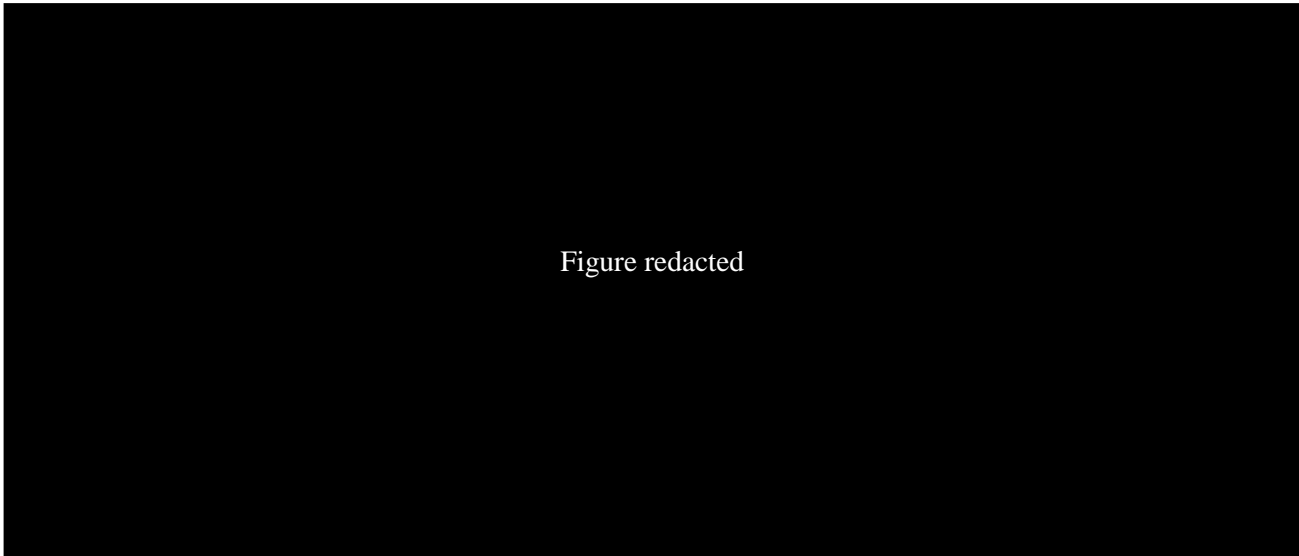


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Figure 6: ERG's cost-effectiveness planes of CBTA + SoC (overall population) versus (i) SoC alone (left side) (ii) glycopyrronium bromide (right side)

Appendix 2: ERG's one-way sensitivity analyses (tornado plots) at the £20,000/QALY threshold. PAS incorporated

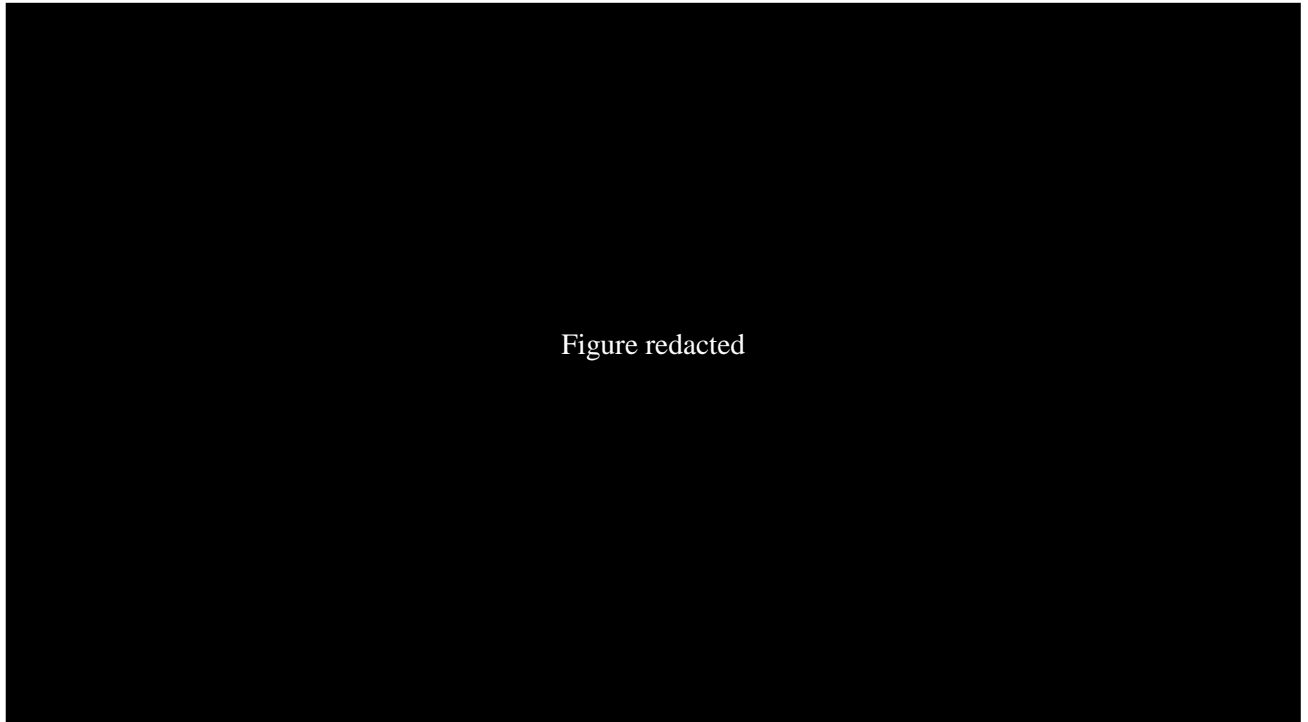


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Figure 7: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

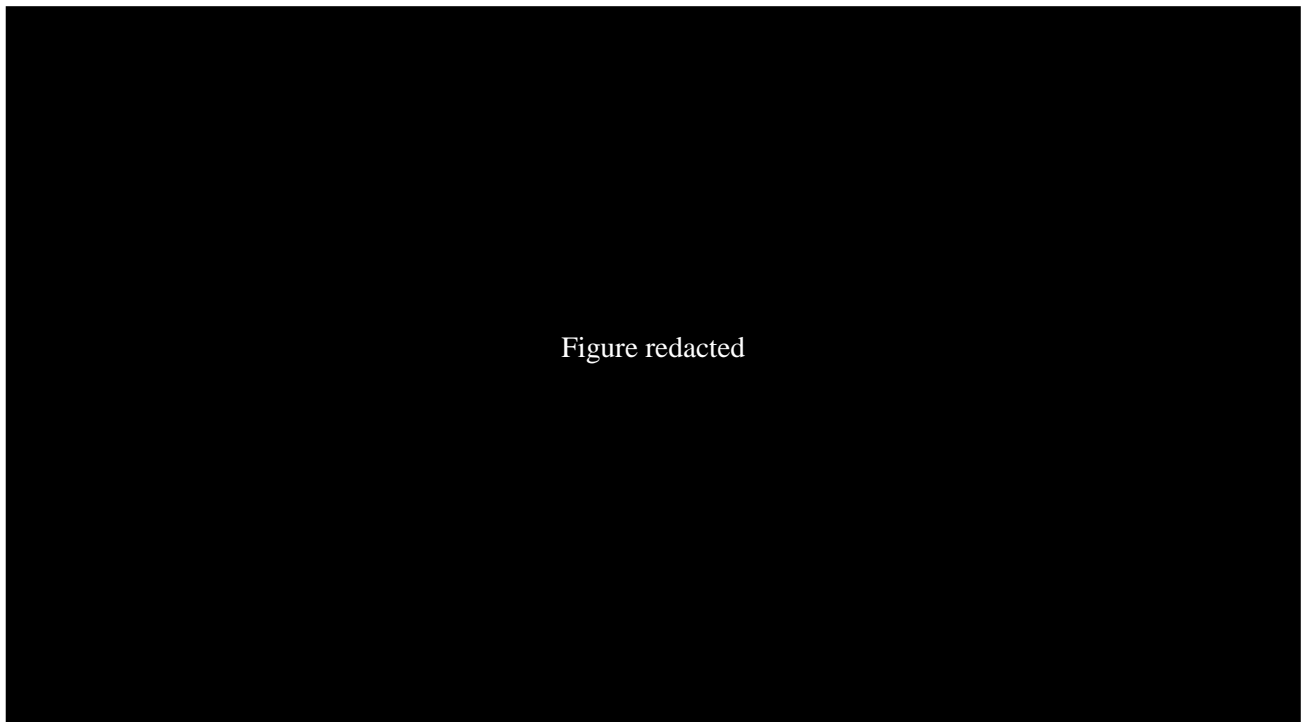


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Figure 8: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

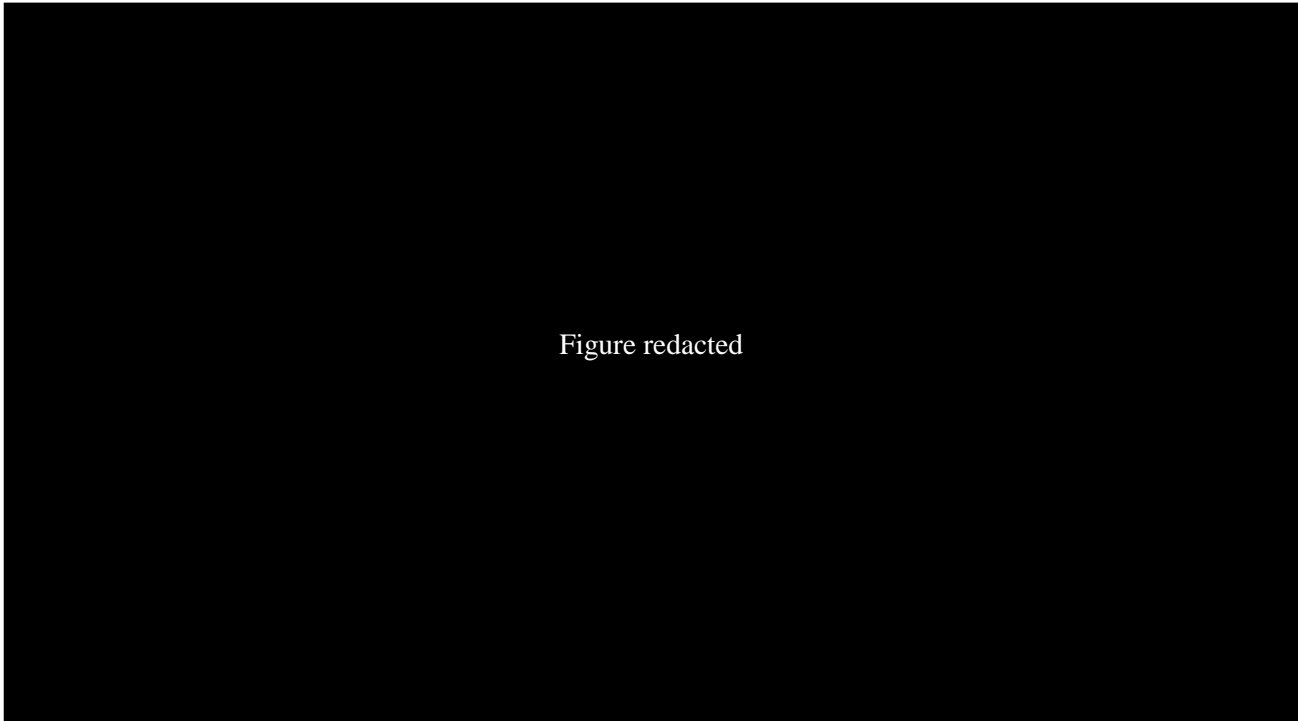
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Figure 9: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

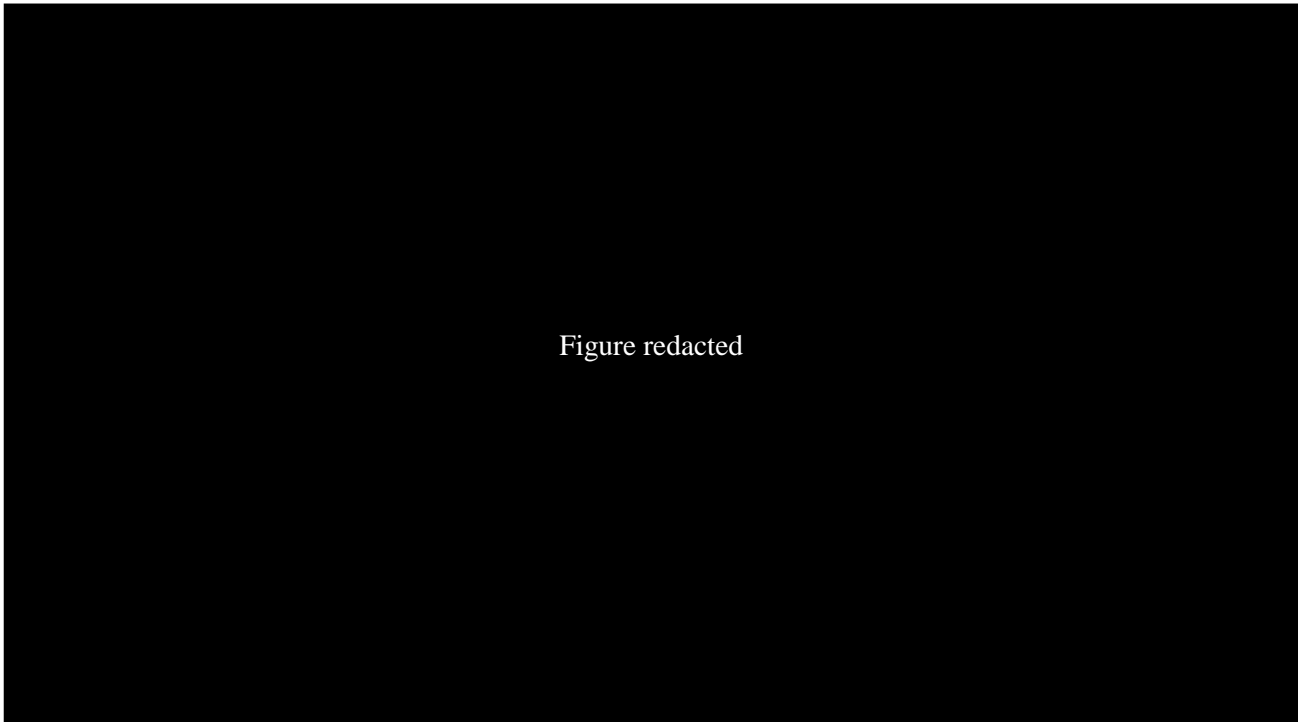
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Figure 10: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

Appendix 3: ERG's one-way sensitivity analyses (tornado plots) at the £30,000/QALY threshold. PAS incorporated

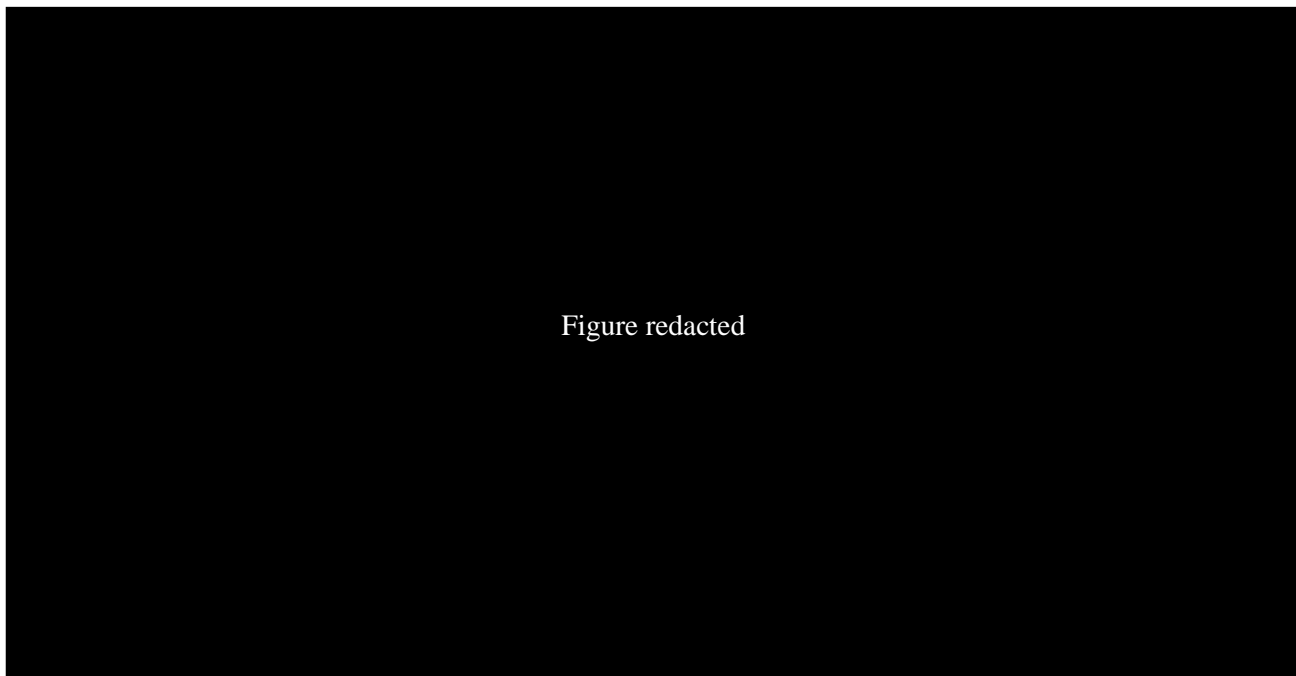


Figure 11: CBTA plus SoC vs. SoC tornado plot (ERG base case - severe patients)

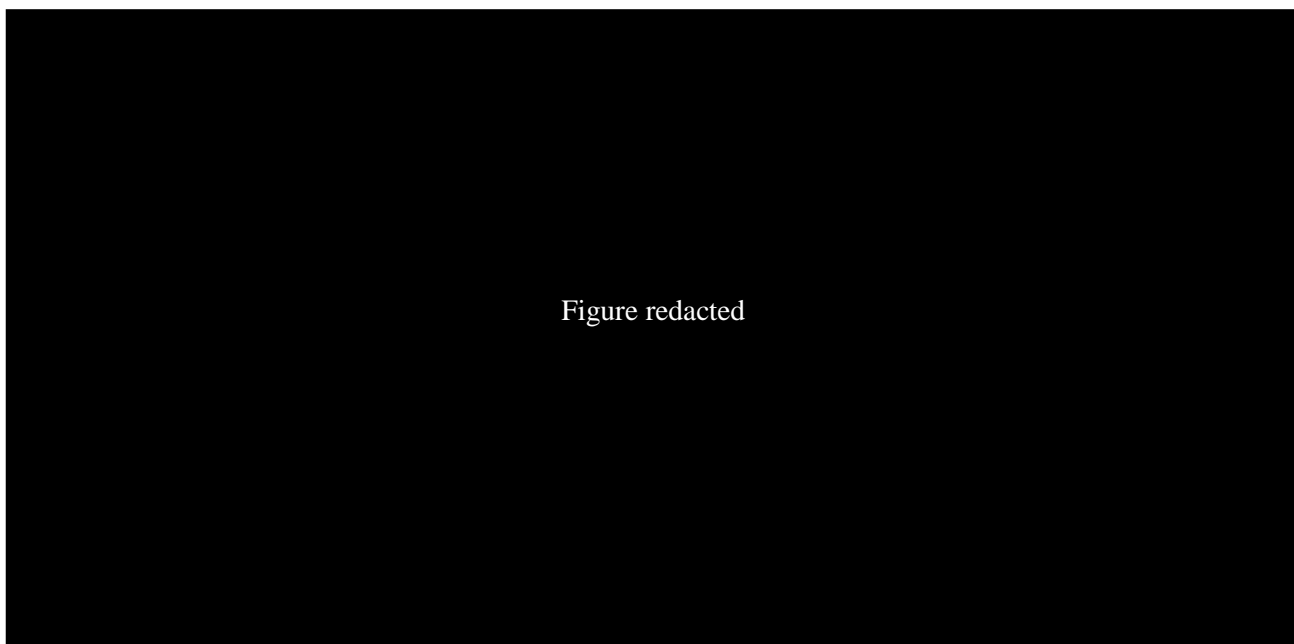


Figure 12: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - severe patients)

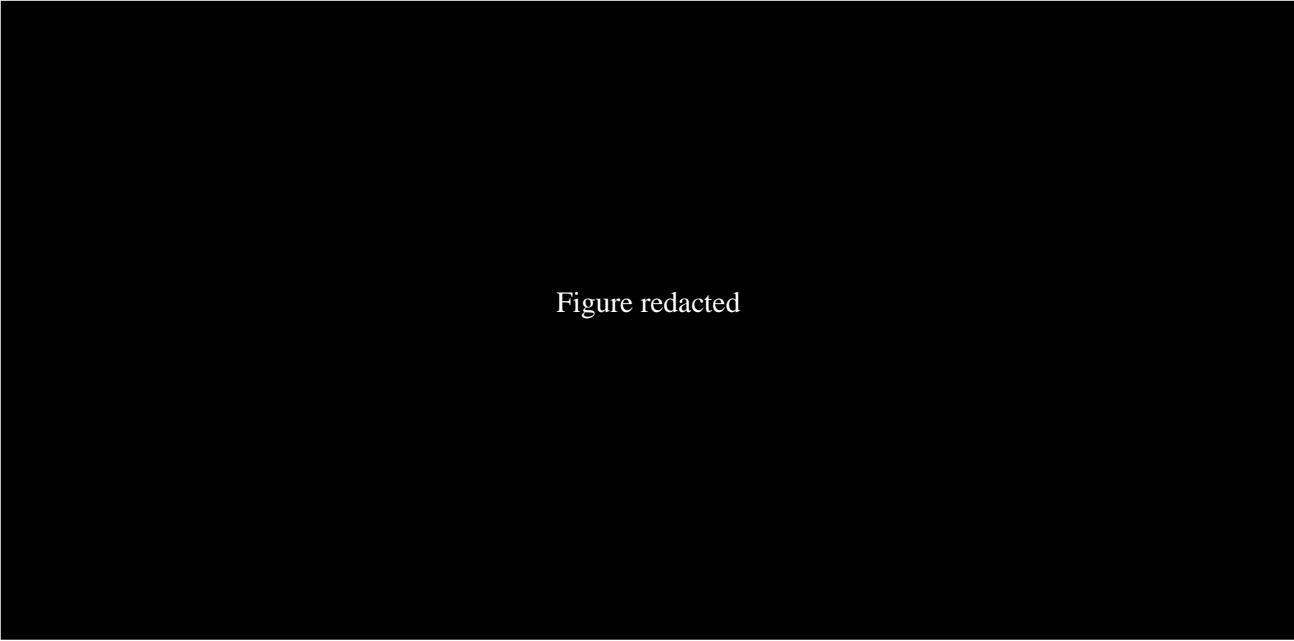


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Figure 13: CBTA plus SoC vs. SoC tornado plot (ERG base case - moderate patients)

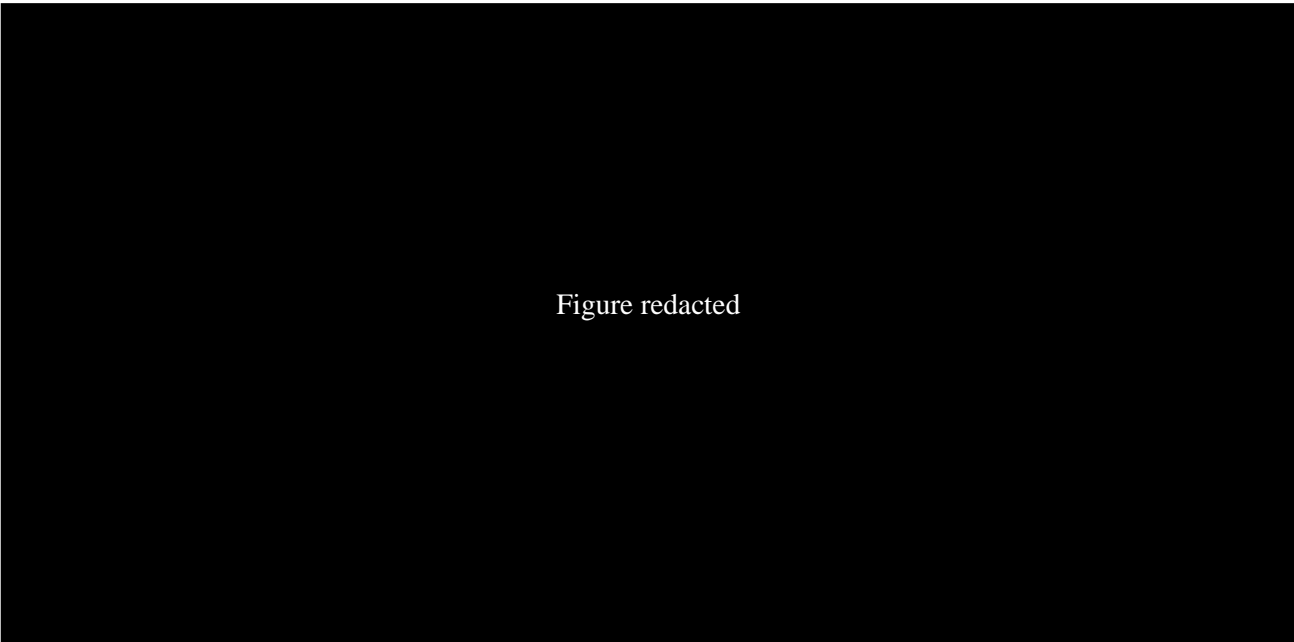


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Figure 14: CBTA plus SoC vs. glycopyrronium bromide tornado plot (ERG base case - moderate patients)

1. Merz Pharma UK Ltd. Clostridium botulinum toxin A for treating chronic sialorrhoea [ID1150]. Company's response to clarification questions from the ERG. 2019.
2. Stevenson M, Ren S, Simpson E, Metry A, Orr M, Wong R. Clostridium botulinum neurotoxin type A for treating chronic sialorrhoea: A Systematic Review; 2019.