

Evaluating Amyloid-Beta as a Surrogate Endpoint for Clinical Function in Alzheimer's Disease

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Background

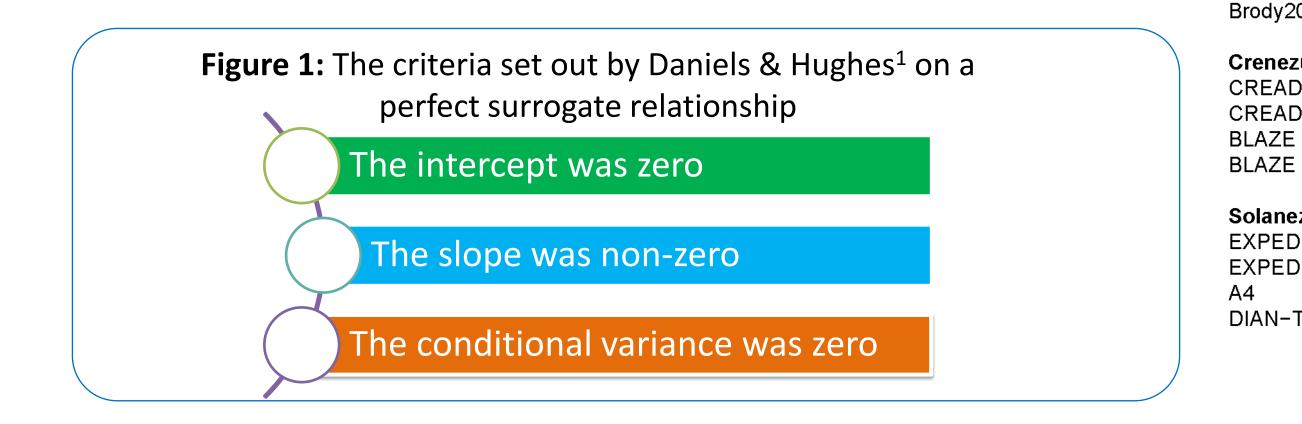
The use of amyloid-beta (Aβ) clearance to support regulatory approvals of drugs in Alzheimer's disease remains controversial. This research aims to evaluate the surrogate **relationship** between **treatment effects on Aβ and clinical** function, measured by Clinical Dementia Rating - Sum Of Boxes (CDR-SOB) using evidence from randomised controlled trials (RCTs) of anti-A β monoclonal antibodies (MABs).

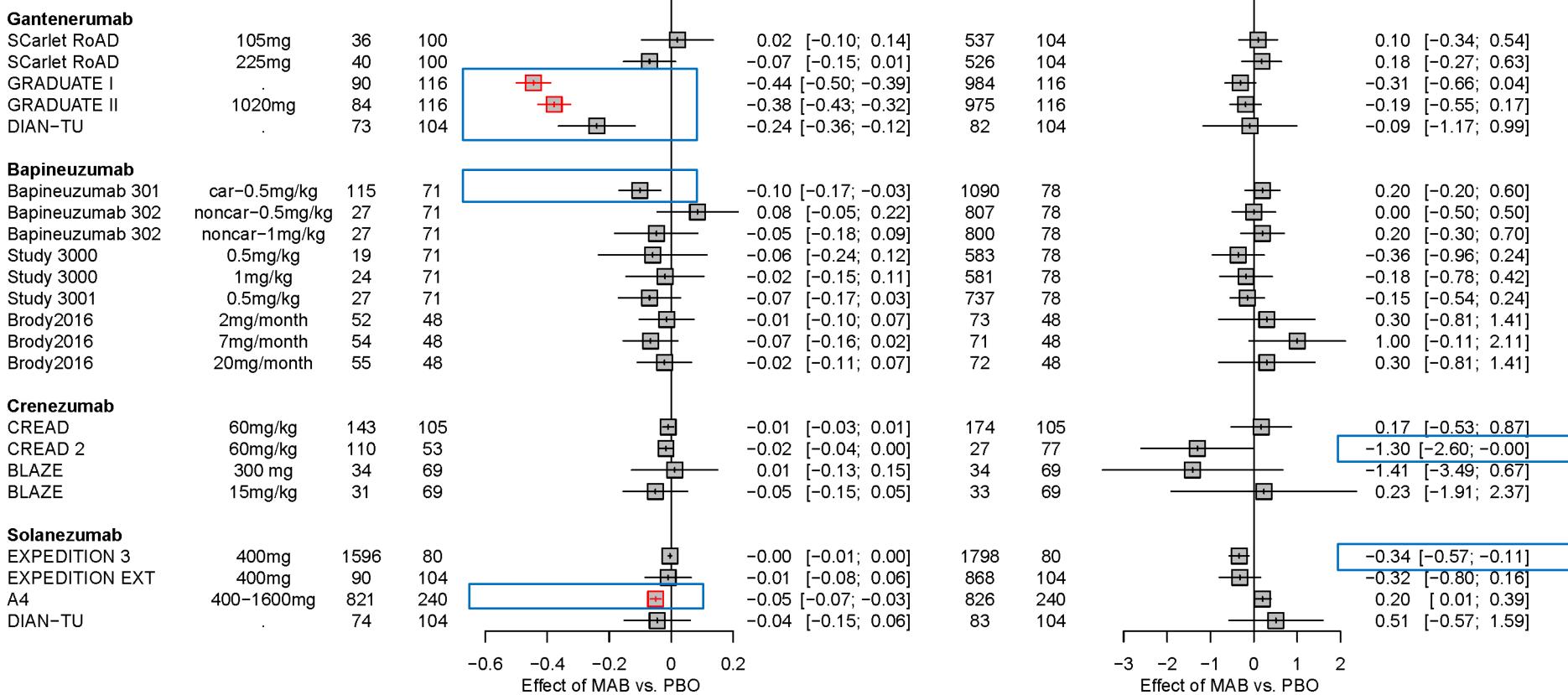
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| Study | Dose | Ν | Timepoint | Amyloid-beta (SUVR) | 95% CI | Ν | Timepoint | CDR-SOB | 95% CI |
|------------------|-------------|------|-----------|---------------------|----------------------|------|-----------|---------------|----------------------|
| Aducanumab | | | | | | | | | |
| EMERGE | low | 193 | 78 | | -0.18 [-0.21; -0.15] | 578 | 78 | | -0.26 [-0.56; 0.04] |
| EMERGE | high | 202 | 78 | <u>₽</u> | -0.28 [-0.31; -0.25] | 587 | 78 | | -0.39 [-0.69; -0.09] |
| ENGAGE | low | 262 | 78 | | -0.17 [-0.19; -0.14] | 664 | 78 | | -0.18 [-0.47; 0.11] |
| ENGAGE | high | 236 | 78 | | -0.23 [-0.26; -0.21] | 628 | 78 | | 0.03 [-0.26; 0.32] |
| PRIME | 1mg/kg | 59 | 54 | 8 | -0.06 [-0.09; -0.04] | 62 | 54 | | -0.06 [-1.12; 1.00] |
| PRIME | 3mg/kg | 64 | 54 | | -0.15 [-0.17; -0.12] | 66 | 54 | — <u> </u> | -0.45 [-1.48; 0.58] |
| PRIME | 6mg/kg | 61 | 54 | | -0.22 [-0.25; -0.20] | 65 | 54 | | -0.68 [-1.74; 0.38] |
| PRIME | Titration | 59 | 54 | | -0.19 [-0.22; -0.15] | 60 | 54 | — <u>B</u> – | -0.73 [-1.79; 0.33] |
| PRIME | 10mg/kg | 54 | 54 | <u>₽</u> | -0.28 [-0.30; -0.25] | 62 | 54 | | -1.08 [-2.23; 0.07] |
| Lecanemab | | | | | | | | | |
| BAN2401-G000-201 | 2.5mg/kg bw | 111 | 79 | | -0.10 [-0.14; -0.05] | 195 | 79 | — | -0.27 [-0.99; 0.45] |
| BAN2401-G000-201 | 5mg/kg mth | 111 | 79 | | -0.14 [-0.18; -0.09] | 197 | 79 | | 0.21 [-0.50; 0.92] |
| BAN2401-G000-201 | 5mg/kg bw | 112 | | | -0.20 [-0.25; -0.16] | 228 | 79 | -6- | -0.04 [-0.61; 0.53] |
| BAN2401-G000-201 | 10mg/kg mth | 170 | 79 | | -0.23 [-0.26; -0.20] | 310 | 79 | | -0.25 [-0.62; 0.12] |
| BAN2401-G000-201 | 10mg/kg bw | 125 | 79 | | -0.31 [-0.35; -0.27] | 245 | 79 | | -0.40 [-0.91; 0.11] |
| Clarity AD | 10mg/kg bw | 415 | | | -0.39 [-0.42; -0.37] | 1471 | | | -0.45 [-0.67; -0.23] |
| Donanemab | | | | | | | | | |
| TRAILBLZAER-ALZ | 700-1400 | 181 | 76 - | | -0.55 [-0.60; -0.51] | 183 | 76 | | -0.36 [-0.83: 0.11] |
| TRAILBLZAER-ALZ | | | | | -0.55 [-0.60; -0.51] | | | | |
| | 700-1400mg | 1304 | | | -0.51 [-0.53; -0.50] | 1270 | 70 | | -0.70 [-0.95; -0.45] |
| | | | | | | | | | |

Figure 2: Forest plot illustrating the treatment effects of MABs versus placebo (PBO) on Aß level and CDR-SOB

Data from RCTs reporting treatment effects on A^β levels and CDR-SOB of MABs were identified through literature review. A Bayesian meta-analysis model¹ was applied, with the intercept, slope and conditional variance parameters quantifying the association. The surrogate relationship for individual treatments was evaluated using subgroup analyses and hierarchical models^{2,3} to borrow information across treatments.





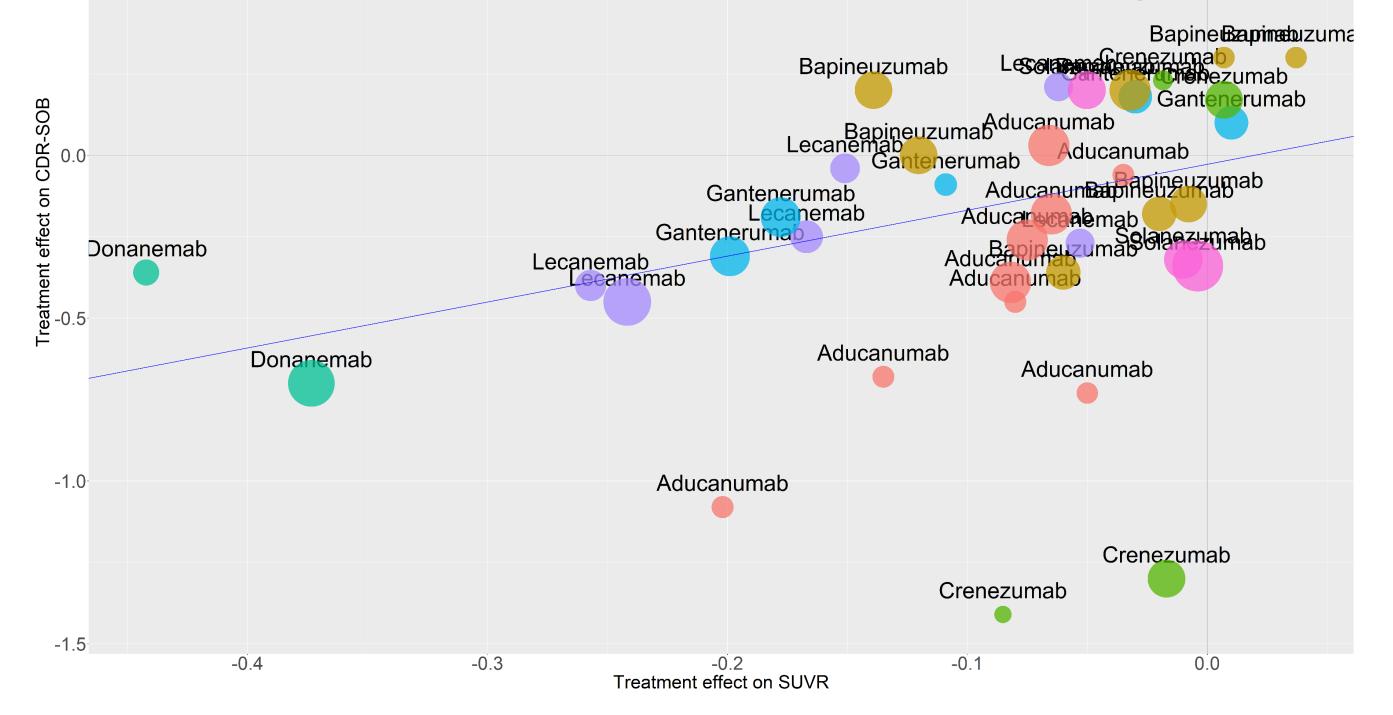
The timepoint is in weeks and the treatment effect is measured by the difference in change from baseline to the follow-up time point vs. placebo (PBO). Estimates in red were imputed by applying a conversion formula based on the radioactive tracer used in the PET scan, where the effect on amyloid-beta was reported on the Centiloid scale alone.

Figure 3: Bubble plot of the overall surrogate relationship between treatment effects on Aβ level and CDR-SOB



Results

1. The review identified 23 RCTs with 39 treatment contrasts (Figure 2) for seven MABs, including aducanumab, bapineuzumab, crenezumab, donanemab,



gantenerumab, lecanemab and solanezumab.

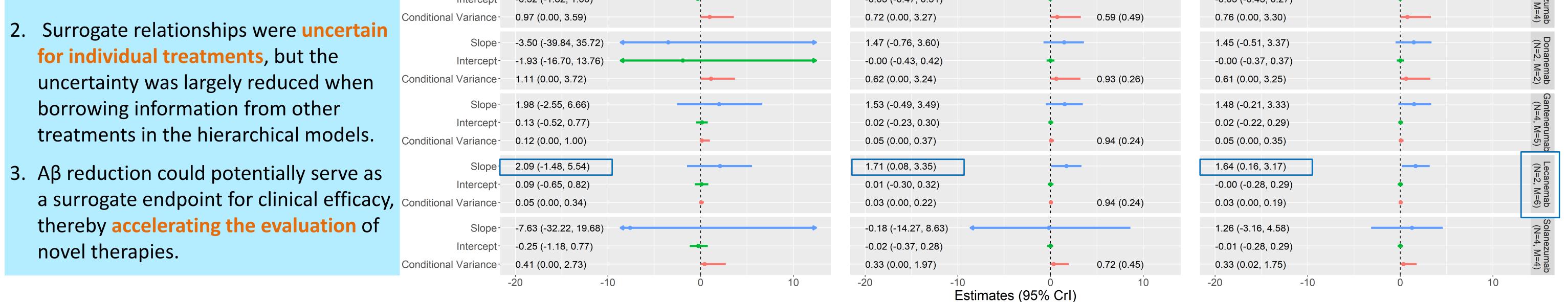
- 2. The overall surrogate relationship (Figure 3) between treatment effects on Aβ level (on the standardised uptake value ratio scale) and CDR-SOB across all MABs was strong: with the close to zero intercept at -0.03 (95% Crl: -0.16, 0.11), a positive slope of 1.41 (95% CrI: 0.6, 2.21) and a small conditional variance of 0.02 (95% Crl: 0, 0.05).
- 3. The results showed large uncertainty around the surrogacy parameters for individual treatments (Figure 4). The use of the hierarchical model reduced the **uncertainty** around the key parameters. The reduction in the width of CrI was 71% (51%-95%) for slope and 28% (7%-65%) for conditional variance, when comparing results from the full-exchangeability model with subgroup analyses.

Figure 4: Forest plot of estimates of slope, intercept and conditional variance for the evaluation of individual surrogate relationship between treatment effects on Aβ level and CDR-SOB

Conclusions

1. The effect on A β level was a good surrogate endpoint for the effect on CDR-SOB when assuming a common surrogate relationship across all included treatments.

| | | Subgroup Analysis | | Partial Exchangeability M | lodel | Full Exchangeability Model | | |
|---|-----------------------|-----------------------|----------------|---------------------------|-------------|----------------------------|---|--------------------------|
| | Slope | 5.57 (-0.82, 11.82) | 2.59 (-0.03, 6 | 6.92) | —— | 2.17 (0.05, 5.69) | | Adu (N= |
| | Intercept- | 0.18 (-0.37, 0.70) | -0.01 (-0.27, | 0.26) | | -0.03 (-0.27, 0.21) | • | Aducanumab (N=3, M=9) |
| | Conditional Variance- | 0.03 (0.00, 0.18) | 0.03 (0.00, 0 | .16) | 0.85 (0.36) | 0.03 (0.00, 0.16) | • | mab =9) |
| 1 | Slope- | -0.46 (-5.76, 5.03) | 0.89 (-3.06, 3 | 3.46) | - | 1.06 (-1.96, 3.30) | • · · · · · · · · · · · · · · · · · · · | Bapin (N= |
| า | Intercept- | 0.02 (-0.35, 0.44) | 0.03 (-0.21, 0 | 0.28) | | 0.03 (-0.19, 0.27) | | ieuzu 5, M |
| | Conditional Variance- | 0.05 (0.00, 0.31) | 0.05 (0.00, 0 | .26) | 0.87 (0.34) | 0.04 (0.00, 0.24) | 1 • • • | umab =9) |
| | Slope- | 11.43 (-25.09, 48.96) | 6.88 (-9.47, 3 | 39.36) | • • • • | 1.74 (-1.83, 5.84) | | Crer (N= |
| | Intercept- | -0.32 (-1.82, 1.00) | -0.03 (-0.47, | 0.31) | | -0.03 (-0.43, 0.27) | • | nezu =4, N |



References

[1] Daniels and Hughes (1997): Meta-analysis for the evaluation of potential surrogate markers. Statistics in Medicine.

[2] Bujkiewicz et al. (2019): NICE DSU Technical Support Document 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints. [3] Papanikos et al. (2020): Bayesian hierarchical meta-analytic methods for modelling surrogate relationships that vary across treatment classes using aggregate data. Statistics in Medicine. This research was funded by the Medical Research Council [MR/T025166/1].