# Comparative EQ-5D-5L Utility Outcomes Across Pegunigalsidase Alfa Regimens and Agalsidase Beta in Adults With Fabry Disease

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## Introduction

- Fabry disease can impair health-related quality of life (HRQoL). Less frequent infusions may reduce treatment burden.[1–3]
- Pegunigalsidase alfa is a PEGylated α-galactosidase A enzyme replacement therapy. Regimens evaluated were 1.0 mg/kg every 2 weeks (E2W) and 2.0 mg/kg every 4 weeks (E4W).[2,3]
- BALANCE (NCT02795676) randomized patients to pegunigalsidase alfa or agalsidase beta E2W. BRIGHT (NCT03180840) and its extension (NCT03614234) evaluated pegunigalsidase alfa E4W without a concurrent control.[2,3,7]
- A targeted search found no direct randomized EQ-5D comparison of pegunigalsidase alfa E4W versus E2W. Population-adjusted cross-trial analyses address this evidence gap.

## Objective

- To compare EQ-5D-5L utility at 1 and 2 years for pegunigalsidase alfa E4W versus agalsidase beta E2W and pegunigalsidase alfa E2W.

## Methods: three approaches to comparison

### Data harmonization and outcome

- Individual patient data from BALANCE and BRIGHT/extension were harmonized. EQ-5D-5L measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Responses were converted to utility scores using the UK value set reported in the analysis. Higher scores mean better health. Data from weeks 52 and 104 were analyzed separately.[4,8]

### Adjustment for differences between trial populations

- Individual patient data from BRIGHT/extension (pegunigalsidase alfa E4W) and BALANCE (pegunigalsidase alfa E2W and agalsidase beta E2W) were used for non-randomized cross-trial comparisons.
- The propensity score model included age, sex and baseline eGFR as covariates to estimate the probability of treatment-group membership.[4]

### Primary analysis (base case): DR-OW

- Doubly robust overlap weighting (DR-OW) gives more weight to comparable patients and also adjusts outcomes for treatment, age, sex and baseline EQ-5D.
- Additional covariates were selected by backward elimination. DR-OW was selected because baseline eGFR differed markedly: it achieved balance on the three propensity score variables and retained more information than DR-SIPW (ESS 27–45 versus 8–18).[4–6]

### Scenario analysis: DR-SIPW

- Doubly robust stabilized inverse probability weighting (DR-SIPW) targets the full population and tests sensitivity to a different weighting approach and target population.
- Poor overlap produced extreme weights, smaller effective sample sizes (ESS) and residual imbalance, supporting its use as a scenario analysis.[4]

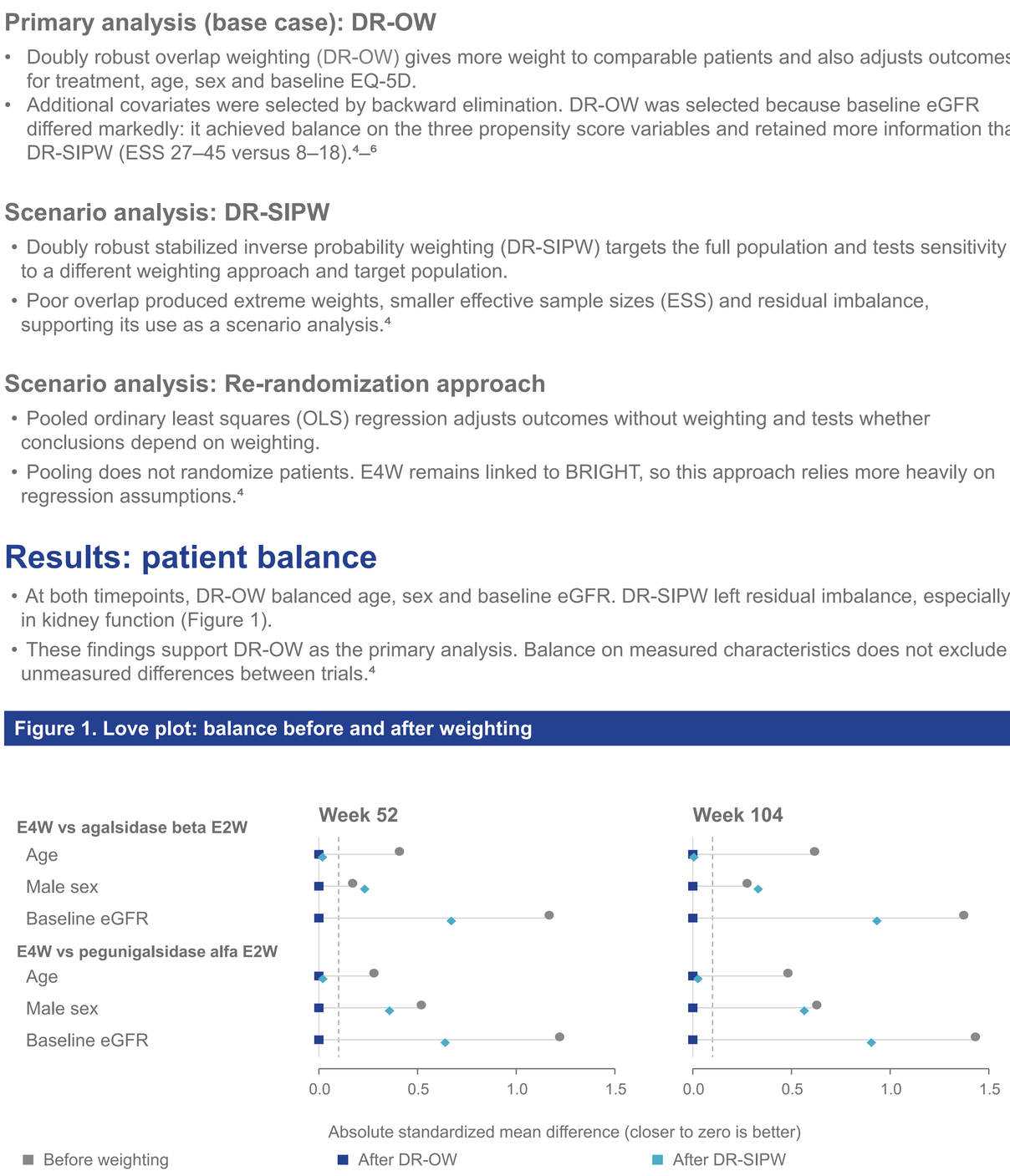
### Scenario analysis: Re-randomization approach

- Pooled ordinary least squares (OLS) regression adjusts outcomes without weighting and tests whether conclusions depend on weighting.
- Pooling does not randomize patients. E4W remains linked to BRIGHT, so this approach relies more heavily on regression assumptions.[4]

## Results: patient balance

- At both timepoints, DR-OW balanced age, sex and baseline eGFR. DR-SIPW left residual imbalance, especially in kidney function (Figure 1).
- These findings support DR-OW as the primary analysis. Balance on measured characteristics does not exclude unmeasured differences between trials.[4]

**Figure 1. Love plot: balance before and after weighting**




How to read: points closer to zero mean more similar patient groups. The dashed line marks |SMD|=0.10. DR-OW balanced all three modeled variables; DR-SIPW left residual imbalance, especially for kidney function.[4]

## Results continued: utility outcomes

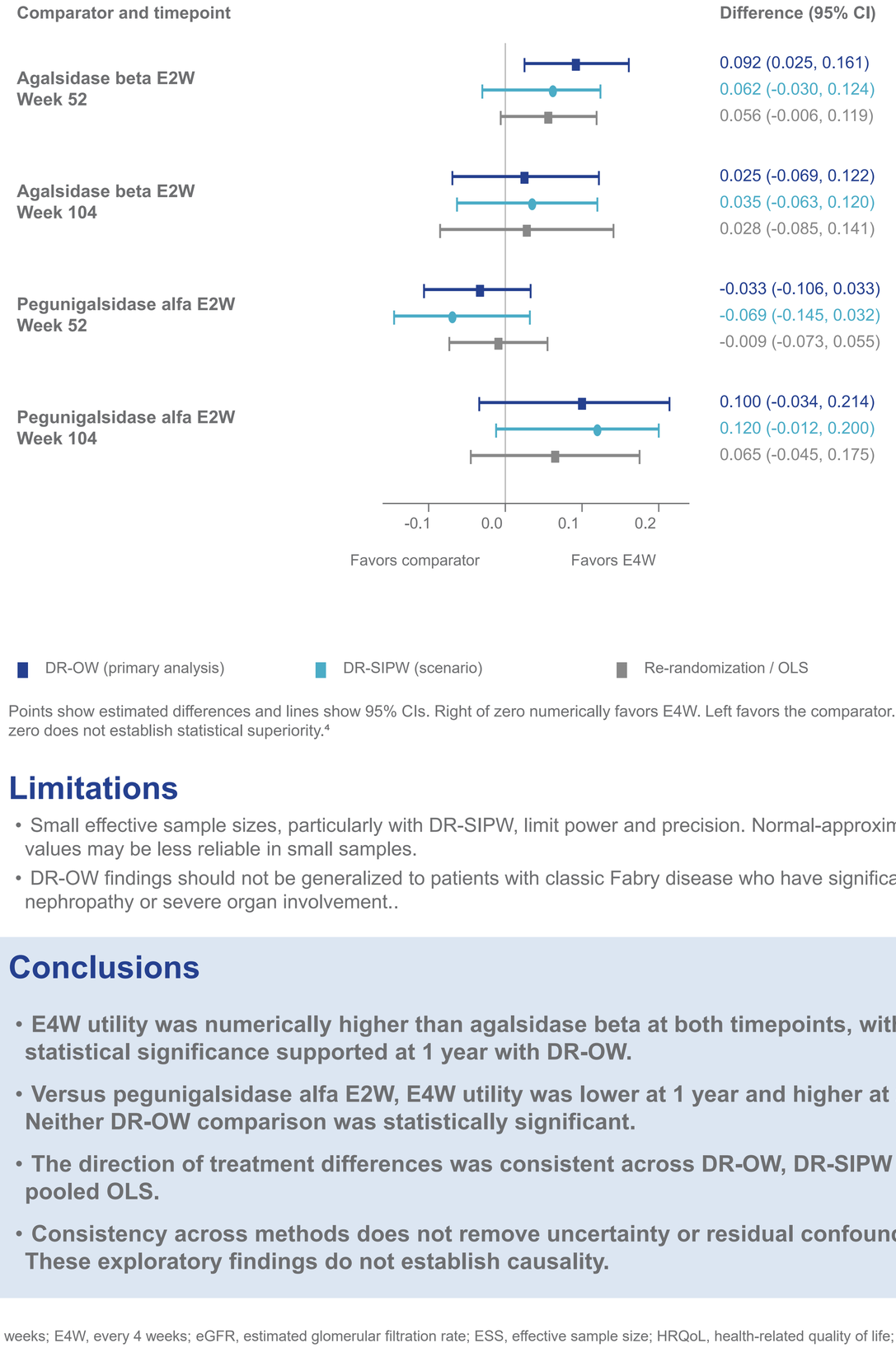
- Utility with pegunigalsidase alfa E4W was numerically higher than agalsidase beta at both timepoints across all three methods. Statistical significance was supported at 1 year with DR-OW only.
- Versus pegunigalsidase alfa E2W, E4W utility was numerically lower at 1 year and higher at 2 years. Neither DR-OW comparison was statistically significant (Table 1, Figure 2).[4]

**Table 1. Adjusted differences, precision and sample size**

| E4W comparator / time | DR-OW<br>Primary analysis | DR-SIPW<br>Scenario | Re-randomization<br>Pooled OLS scenario |
|---|---|---|---|
| Agalsidase beta E2W<br>1 year (Week 52) | **0.092; p=0.016<br>(0.025, 0.161)<br>ESS=33.9** | 0.062; p=0.109<br>(−0.030, 0.124)<br>ESS=11.4 | 0.056; p=0.076<br>(−0.006, 0.119)<br>N=51 (unweighted) |
| Agalsidase beta E2W<br>2 years (Week 104) | 0.025; p=0.650<br>(−0.069, 0.122)<br>ESS=26.7 | 0.035; p=0.463<br>(−0.063, 0.120)<br>ESS=8.1 | 0.028; p=0.621<br>(−0.085, 0.141)<br>N=46 (unweighted) |
| Pegunigalsidase alfa E2W<br>1 year (Week 52) | −0.033; p=0.346<br>(−0.106, 0.033)<br>ESS=44.7 | −0.069; p=0.113<br>(−0.145, 0.032)<br>ESS=17.7 | −0.009; p=0.787<br>(−0.073, 0.055)<br>N=73 (unweighted) |
| Pegunigalsidase alfa E2W<br>2 years (Week 104) | 0.100; p=0.109<br>(−0.034, 0.214)<br>ESS=34.8 | 0.120; p=0.031*<br>(−0.012, 0.200)<br>ESS=16.3 | 0.065; p=0.244<br>(−0.045, 0.175)<br>N=70 (unweighted) |

Estimate-cell colors: light green = numerically higher utility with E4W, without statistical significance by the CI criterion. Dark green = statistically significantly higher utility with E4W (p<0.05 and CI excludes zero). White = numerically lower utility with E4W (none statistically significant).
Values are differences (95% CI). OLS uses unweighted N rather than ESS.[4] *p=0.031 uses a normal approximation, whereas the bootstrap CI includes zero. Statistical significance is therefore not supported by the bootstrap CI.

**Figure 2. Adjusted utility differences across methods**




Points show estimated differences and lines show 95% CIs. Right of zero numerically favors E4W. Left favors the comparator. A CI crossing zero does not establish statistical superiority.[4]

## Limitations

- Small effective sample sizes, particularly with DR-SIPW, limit power and precision. Normal-approximation p-values may be less reliable in small samples.
- DR-OW findings should not be generalized to patients with classic Fabry disease who have significant nephropathy or severe organ involvement..

## Conclusions

- **E4W utility was numerically higher than agalsidase beta at both timepoints, with statistical significance supported at 1 year with DR-OW.**
- **Versus pegunigalsidase alfa E2W, E4W utility was lower at 1 year and higher at 2 years. Neither DR-OW comparison was statistically significant.**
- **The direction of treatment differences was consistent across DR-OW, DR-SIPW and pooled OLS.**
- **Consistency across methods does not remove uncertainty or residual confounding. These exploratory findings do not establish causality.**

Abbreviations: CI, confidence interval; DR-OW, doubly robust overlap weighting; DR-SIPW, doubly robust stabilized inverse probability weighting; E2W, every 2 weeks; E4W, every 4 weeks; eGFR, estimated glomerular filtration rate; ESS, effective sample size; HRQoL, health-related quality of life; OLS, ordinary least squares; SMD, standardized mean difference; UPCR, urine protein-to-creatinine ratio.

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