

## **SUPPLEMENTAL MATERIAL**

### **Overall disability response score: an integrated endpoint to assess disability improvement and worsening over time in patients with multiple sclerosis**

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**Supplementary Table 1. Analysis of ODRS by visit in AFFIRM study**

|                               | AFFIRM (RRMS)     |                 |
|-------------------------------|-------------------|-----------------|
|                               | Natalizumab       | Placebo         |
| <i>n</i>                      | <b>627</b>        | <b>312</b>      |
| Week 12                       |                   |                 |
| <i>n</i>                      | 608               | 299             |
| Mean (SD)                     | −0.1 (0.86)       | −0.2 (0.83)     |
| Median (Q1, Q3)               | 0.0 (0.0, 0.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.07             | −0.21           |
| Treatment difference (95% CI) | 0.14 (0.03, 0.26) |                 |
| <i>p</i> value                | 0.017             |                 |
| Week 24                       |                   |                 |
| <i>n</i>                      | 602               | 294             |
| Mean (SD)                     | 0.0 (0.98)        | −0.3 (1.01)     |
| Median (Q1, Q3)               | 0.0 (0.0, 0.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.04             | −0.28           |
| Treatment difference (95% CI) | 0.24 (0.11, 0.38) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 36                       |                   |                 |
| <i>n</i>                      | 592               | 291             |
| Mean (SD)                     | −0.1 (1.06)       | −0.3 (1.17)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 0.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.10             | −0.35           |
| Treatment difference (95% CI) | 0.25 (0.10, 0.40) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 48                       |                   |                 |
| <i>n</i>                      | 590               | 285             |
| Mean (SD)                     | 0.0 (1.15)        | −0.3 (1.17)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.02             | −0.33           |
| Treatment difference (95% CI) | 0.31 (0.14, 0.47) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 60                       |                   |                 |
| <i>n</i>                      | 584               | 284             |
| Mean (SD)                     | 0.0 (1.16)        | −0.4 (1.25)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | 0.02              | −0.39           |

|                               |                   |                 |
|-------------------------------|-------------------|-----------------|
| Treatment difference (95% CI) | 0.41 (0.24, 0.57) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 72                       |                   |                 |
| <i>n</i>                      | 576               | 282             |
| Mean (SD)                     | 0.0 (1.13)        | −0.4 (1.33)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.02             | −0.43           |
| Treatment difference (95% CI) | 0.40 (0.23, 0.57) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 84                       |                   |                 |
| <i>n</i>                      | 575               | 280             |
| Mean (SD)                     | 0.0 (1.20)        | −0.5 (1.29)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.05             | −0.50           |
| Treatment difference (95% CI) | 0.45 (0.28, 0.63) |                 |
| <i>p</i> value                | <0.001            |                 |
| Week 96                       |                   |                 |
| <i>n</i>                      | 571               | 274             |
| Mean (SD)                     | 0.0 (1.26)        | −0.4 (1.39)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)   | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.03             | −0.51           |
| Treatment difference (95% CI) | 0.48 (0.30, 0.67) |                 |
| <i>p</i> value                | <0.001            |                 |

CI: confidence interval; ITT: intent-to-treat; ODRS: Overall Disability Response Score; Q1: quartile 1; Q3: quartile 3; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation.

Adjusted means and 95% CIs for each treatment group, treatment differences (Active vs. Placebo), 95% CIs and *p*-values are based on the Mixed Model for Repeated Measures (MMRM) adjusted for baseline EDSS, T25FW and 9HPT (average of 2 hands).

**Supplementary Table 2. Analysis of ODRS by visit in ASCEND study**

|                               | ASCEND (SPMS)      |                 |
|-------------------------------|--------------------|-----------------|
|                               | Natalizumab        | Placebo         |
| <i>n</i>                      | <b>439</b>         | <b>448</b>      |
| Week 12                       |                    |                 |
| <i>n</i>                      | 415                | 411             |
| Mean (SD)                     | −0.1 (1.12)        | −0.2 (1.03)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.05              | −0.19           |
| Treatment difference (95% CI) | 0.14 (−0.00, 0.29) |                 |
| <i>p</i> value                | 0.055              |                 |
| Week 24                       |                    |                 |
| <i>n</i>                      | 399                | 394             |
| Mean (SD)                     | −0.1 (1.22)        | −0.2 (1.22)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.16              | −0.21           |
| Treatment difference (95% CI) | 0.04 (−0.13, 0.21) |                 |
| <i>p</i> value                | 0.613              |                 |
| Week 36                       |                    |                 |
| <i>n</i>                      | 390                | 373             |
| Mean (SD)                     | −0.2 (1.36)        | −0.3 (1.35)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−1.0, 1.0) |
| Adjusted mean                 | −0.26              | −0.34           |
| Treatment difference (95% CI) | 0.08 (−0.11, 0.27) |                 |
| <i>p</i> value                | 0.382              |                 |
| Week 48                       |                    |                 |
| <i>n</i>                      | 377                | 354             |
| Mean (SD)                     | −0.3 (1.39)        | −0.3 (1.34)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.26              | −0.44           |
| Treatment difference (95% CI) | 0.18 (−0.02, 0.37) |                 |
| <i>p</i> value                | 0.076              |                 |
| Week 60                       |                    |                 |
| <i>n</i>                      | 348                | 337             |
| Mean (SD)                     | −0.3 (1.47)        | −0.4 (1.44)     |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.35              | −0.51           |

|                               |                    |                  |
|-------------------------------|--------------------|------------------|
| Treatment difference (95% CI) | 0.16 (−0.06, 0.37) |                  |
| <i>p</i> value                | 0.148              |                  |
| Week 72                       |                    |                  |
| <i>n</i>                      | 342                | 325              |
| Mean (SD)                     | −0.2 (1.47)        | −0.5 (1.47)      |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | −1.0 (−1.0, 0.0) |
| Adjusted mean                 | −0.29              | −0.62            |
| Treatment difference (95% CI) | 0.33 (0.12, 0.54)  |                  |
| <i>p</i> value                | 0.003              |                  |
| Week 84                       |                    |                  |
| <i>n</i>                      | 325                | 317              |
| Mean (SD)                     | −0.4 (1.42)        | −0.5 (1.54)      |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | 0.0 (−2.0, 0.0)  |
| Adjusted mean                 | −0.45              | −0.66            |
| Treatment difference (95% CI) | 0.21 (−0.01, 0.43) |                  |
| <i>p</i> value                | 0.064              |                  |
| Week 96                       |                    |                  |
| <i>n</i>                      | 325                | 305              |
| Mean (SD)                     | −0.4 (1.57)        | −0.6 (1.60)      |
| Median (Q1, Q3)               | 0.0 (−1.0, 1.0)    | −1.0 (−2.0, 0.0) |
| Adjusted mean                 | −0.45              | −0.79            |
| Treatment difference (95% CI) | 0.34 (0.10, 0.58)  |                  |
| <i>p</i> value                | 0.005              |                  |

CI: confidence interval; ITT: intent-to-treat; ODRS: Overall Disability Response Score; Q1: quartile 1; Q3: quartile 3; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

Adjusted means and 95% CIs for each treatment group, treatment differences (Active vs. Placebo), 95% CIs and *p*-values are based on the Mixed Model for Repeated Measures (MMRM) adjusted for baseline EDSS, T25FW and 9HPT (average of 2 hands).

**Supplementary Table 3. ODRS analysis in AFFIRM and ASCEND studies (20% change threshold for T25FW and 9HPT)**

|                                       | AFFIRM (RRMS)     |            | ASCEND (SPMS)     |            |
|---------------------------------------|-------------------|------------|-------------------|------------|
|                                       | Natalizumab       | Placebo    | Natalizumab       | Placebo    |
| <i>n</i>                              | <b>627</b>        | <b>312</b> | <b>439</b>        | <b>448</b> |
| Mean change over Week 96 <sup>a</sup> | −0.04             | −0.33      | −0.32             | −0.47      |
| Treatment difference (95% CI)         | 0.29 (0.19, 0.39) |            | 0.15 (0.01, 0.29) |            |
| <i>p</i> value                        | < 0.001           |            | 0.031             |            |
| Mean change at Week 96 <sup>a</sup>   | −0.06             | −0.50      | −0.48             | −0.75      |
| Treatment difference (95% CI)         | 0.44 (0.28, 0.59) |            | 0.27 (0.06, 0.48) |            |
| <i>p</i> value                        | < 0.001           |            | 0.013             |            |
| Slope of change per year <sup>b</sup> | −0.00             | −0.19      | −0.18             | −0.30      |
| Treatment difference (95% CI)         | 0.19 (0.14, 0.24) |            | 0.12 (0.06, 0.18) |            |
| <i>p</i> value                        | < 0.001           |            | < 0.001           |            |

9HPT-D: 9-Hole Peg Test, dominant hand; 9HPT-ND: 9-Hole Peg Test, non-dominant hand; CI: confidence interval; EDSS Expanded Disability Status Scale; ODRS: Overall Disability Response Score; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: Timed 25-foot Walk.

<sup>a</sup>Adjusted means and 95% CIs for each treatment group, treatment differences (active vs. placebo), 95% CIs and *p* values are based on the Mixed Model for Repeated Measures adjusted for baseline EDSS, T25FW, and 9HPT (average of two hands).

<sup>b</sup>Adjusted means and 95% CIs for each treatment group, treatment differences (active vs. placebo), 95% CIs and *p* values are based on the mixed-effect model of treatment and time (numerical) interaction as fixed effect, individual intercept (at Week 12) as random effect, and baseline EDSS, T25FW, and 9HPT (average of two hands) as covariates.

**Supplementary Table 4. ODRS analysis in AFFIRM and ASCEND studies (20% change threshold for T25FW and 9HPT; 50% weight 9HPT-D and 9HPT-ND)**

|                                       | AFFIRM (RRMS)     |            | ASCEND (SPMS)      |            |
|---------------------------------------|-------------------|------------|--------------------|------------|
|                                       | Natalizumab       | Placebo    | Natalizumab        | Placebo    |
| <i>n</i>                              | <b>627</b>        | <b>312</b> | <b>439</b>         | <b>448</b> |
| Mean change over Week 96 <sup>a</sup> | −0.02             | −0.26      | −0.30              | −0.40      |
| Treatment difference (95% CI)         | 0.24 (0.16, 0.33) |            | 0.10 (−0.01, 0.21) |            |
| <i>p</i> value                        | < 0.001           |            | 0.084              |            |
| Mean change at Week 96 <sup>a</sup>   | −0.05             | −0.42      | −0.47              | −0.64      |
| Treatment difference (95% CI)         | 0.37 (0.23, 0.50) |            | 0.17 (0.00, 0.34)  |            |
| <i>p</i> value                        | < 0.001           |            | 0.048              |            |
| Slope of change per year <sup>b</sup> | −0.00             | −0.16      | −0.17              | −0.26      |
| Treatment difference (95% CI)         | 0.16 (0.12, 0.20) |            | 0.08 (0.03, 0.13)  |            |
| <i>p</i> value                        | < 0.001           |            | 0.0013             |            |

9HPT-D: 9-Hole Peg Test, dominant hand; 9HPT-ND: 9-Hole Peg Test, non-dominant hand; CI: confidence interval; ODRS: Overall Disability Response Score; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: Timed 25-foot Walk.

<sup>a</sup>Adjusted means and 95% CIs for each treatment group, treatment differences (active vs. placebo), 95% CIs and *p* values are based on the Mixed Model for Repeated Measures adjusted for baseline EDSS, T25FW, and 9HPT (average of two hands).

<sup>b</sup>Adjusted means and 95% CIs for each treatment group, treatment differences (active vs. placebo), 95% CIs and *p* values are based on the mixed-effect model of treatment and time (numerical) interaction as fixed effect, individual intercept (at Week 12) as random effect, and baseline EDSS, T25FW, and 9HPT (average of two hands) as covariates.

**Supplementary Table 5. EDSS analysis in AFFIRM and ASCEND**

|                               | EDSS                 |            |                     |            |
|-------------------------------|----------------------|------------|---------------------|------------|
|                               | AFFIRM (RRMS)        |            | ASCEND (SPMS)       |            |
|                               | Natalizumab          | Placebo    | Natalizumab         | Placebo    |
| <i>n</i>                      | <b>627</b>           | <b>312</b> | <b>439</b>          | <b>448</b> |
| Mean EDSS at 12 weeks         | 2.26                 | 2.33       | 5.59                | 5.56       |
| Treatment difference (95% CI) | −0.07 (−0.16, 0.02)  |            | 0.03 (−0.03, 0.09)  |            |
| <i>p</i> value                | 0.110                |            | 0.293               |            |
| Mean EDSS at Week 24          | 2.26                 | 2.40       | 5.60                | 5.53       |
| Treatment difference (95% CI) | −0.14 (−0.24, −0.04) |            | 0.07 (0.01, 0.13)   |            |
| <i>p</i> value                | 0.006                |            | 0.031               |            |
| Mean EDSS at Week 36          | 2.24                 | 2.49       | 5.57                | 5.57       |
| Treatment difference (95% CI) | −0.25 (−0.36, −0.14) |            | −0.01 (−0.08, 0.07) |            |
| <i>p</i> value                | <0.001               |            | 0.884               |            |
| Mean EDSS at Week 48          | 2.21                 | 2.48       | 5.58                | 5.61       |
| Treatment difference (95% CI) | −0.27 (−0.38, −0.15) |            | −0.04 (−0.12, 0.05) |            |
| <i>p</i> value                | < 0.001              |            | 0.364               |            |
| Mean EDSS at Week 60          | 2.21                 | 2.47       | 5.61                | 5.60       |
| Treatment difference (95% CI) | −0.25 (−0.37, −0.13) |            | 0.01 (−0.07, 0.10)  |            |
| <i>p</i> value                | < 0.001              |            | 0.768               |            |



|                               |                      |      |                     |      |
|-------------------------------|----------------------|------|---------------------|------|
| Mean EDSS at Week 72          | 2.26                 | 2.54 | 5.61                | 5.66 |
| Treatment difference (95% CI) | −0.28 (−0.41, −0.15) |      | −0.05 (−0.14, 0.04) |      |
| <i>p</i> value                | < 0.001              |      | 0.310               |      |
| Mean EDSS at Week 84          | 2.22                 | 2.60 | 5.62                | 5.63 |
| Treatment difference (95% CI) | 0.38 (−0.51, −0.25)  |      | −0.01 (−0.11, 0.09) |      |
| <i>p</i> value                | < 0.001              |      | 0.841               |      |
| Mean EDSS at Week 96          | 2.24                 | 2.61 | 5.68                | 5.68 |
| Treatment difference (95% CI) | −0.37 (−0.50, −0.23) |      | 0.01 (−0.09, 0.11)  |      |
| <i>p</i> value                | < 0.001              |      | 0.878               |      |
| Mean EDSS over 96 weeks       | 2.24                 | 2.49 | 5.61                | 5.60 |
| Treatment difference (95% CI) | −0.25 (−0.34, −0.16) |      | 0.00 (−0.07, 0.07)  |      |
| <i>p</i> value                | < 0.001              |      | 0.946               |      |

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9HPT: 9-Hole Peg Test; CI: confidence interval; EDSS: Expanded Disability Status Scale; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; T25FW: Timed 25-Foot Walk.

Adjusted means and 95% CIs for each treatment group, treatment differences (Active vs. Placebo), 95% CIs and *p* values are based on the Mixed Model for Repeated Measures adjusted for baseline EDSS, T25FW, and 9HPT (average of two hands).

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**Supplementary Table 6. MSFC Visit in AFFIRM**

|                               | AFFIRM (RRMS)      |            |
|-------------------------------|--------------------|------------|
|                               | Natalizumab        | Placebo    |
| <i>n</i>                      | <b>627</b>         | <b>312</b> |
| Mean MSFC-z score at 12 weeks | 0.19               | 0.13       |
| Treatment difference (95% CI) | 0.05 (0.00, 0.11)  |            |
| <i>p</i> value                | 0.045              |            |
| Mean MSFC-z score at Week 24  | 0.20               | 0.16       |
| Treatment difference (95% CI) | 0.04 (−0.01, 0.09) |            |
| <i>p</i> value                | 0.111              |            |
| Mean MSFC-z score at Week 36  | 0.20               | 0.13       |
| Treatment difference (95% CI) | 0.07 (0.02, 0.13)  |            |
| <i>p</i> value                | 0.010              |            |
| Mean MSFC-z score at Week 48  | 0.23               | 0.17       |
| Treatment difference (95% CI) | 0.06 (0.01, 0.12)  |            |
| <i>p</i> value                | 0.020              |            |
| Mean MSFC-z score at Week 60  | 0.25               | 0.17       |
| Treatment difference (95% CI) | 0.07 (0.02, 0.13)  |            |
| <i>p</i> value                | 0.006              |            |
| Mean MSFC-z score at Week 72  | 0.25               | 0.18       |

|                                 |      |                    |      |
|---------------------------------|------|--------------------|------|
| Treatment difference (95% CI)   |      | 0.08 (0.02, 0.13)  |      |
| <i>p</i> value                  |      | 0.004              |      |
| Mean MSFC-z score at Week 84    | 0.26 |                    | 0.16 |
| Treatment difference (95% CI)   |      | 0.11 (0.05, 0.16)  |      |
| <i>p</i> value                  |      | <0.001             |      |
| Mean MSFC-z score at Week 96    | 0.22 |                    | 0.17 |
| Treatment difference (95% CI)   |      | 0.05 (−0.10, 0.21) |      |
| <i>p</i> value                  |      | 0.518              |      |
| Mean MSFC-z score over 96 weeks | 0.23 |                    | 0.16 |
| Treatment difference (95% CI)   |      | 0.07 (0.02, 0.12)  |      |
| <i>p</i> value                  |      | 0.011              |      |

9HPT: 9-Hole Peg Test; EDSS: Expanded Disability Status Scale; MSFC: Multiple Sclerosis Functional Composite; PASAT 3: Paced Auditory Serial Addition Test 3; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; T25FW: Timed 25-Foot Walk.

<sup>a</sup>Adjusted means and 95% CIs for each treatment group, treatment differences (Active vs. Placebo), 95% CIs and *p* values are based on the Mixed Model for Repeated Measures adjusted for baseline EDSS, T25FW, and 9HPT (average of two hands).

<sup>b</sup>Z-scores were calculated based on a reference population mean of 5.328 and a SD of 2.005 for the T25FW, a mean of 0.050 and a SD of 0.010 for the 9HPT, and a mean of 50.824 and a SD of 10.304 for the PASAT 3.

**Supplementary Table 7. Summary of correlations between ODRS and mean change from baseline in SF-36 or MSIS-29 at 2 years.**

| PRO (change from baseline)                      | AFFIRM             |              | ASCEND             |              |                      |                     |
|---|--------------------|--------------|--------------------|--------------|----------------------|---------------------|
|   | SF-36 <sup>a</sup> |              | SF-36 <sup>a</sup> |              | MSIS-29 <sup>b</sup> |                     |
|   | PCS                | MCS          | PCS                | MCS          | Physical score       | Psychological score |
| Mean change (SE) associated with ODRS $\geq 3$  | 8.87 (1.98)        | 9.06 (2.67)  | 3.22 (1.53)        | 6.50 (2.28)  | -13.85 (4.16)        | -17.30 (4.35)       |
| <i>p</i> value                                  | < 0.001            | < 0.001      | 0.035              | 0.004        | < 0.001              | < 0.001             |
| Mean change (SE) associated with ODRS = 2       | 2.93 (1.18)        | 5.40 (1.59)  | 0.73 (1.16)        | 6.33 (1.73)  | -9.57 (3.17)         | -8.42 (3.31)        |
| <i>p</i> value                                  | 0.013              | < 0.001      | 0.531              | < 0.001      | 0.003                | 0.011               |
| Mean change (SE) associated with ODRS = 1       | 1.66 (0.67)        | 2.69 (0.91)  | 1.29 (0.73)        | 1.95 (1.09)  | -5.08 (1.97)         | -7.75 (2.06)        |
| <i>p</i> value                                  | 0.014              | 0.003        | 0.077              | 0.073        | 0.010                | < 0.001             |
| Mean change (SE) associated with ODRS = 0       | 0.40 (0.46)        | 1.52 (0.62)  | 1.11 (0.57)        | 0.12 (0.85)  | -1.85 (1.52)         | -3.47 (1.59)        |
| <i>p</i> value                                  | 0.381              | 0.014        | 0.051              | 0.888        | 0.225                | 0.029               |
| Mean change (SE) associated with ODRS = -1      | -0.86 (0.63)       | -0.76 (0.85) | -0.17 (0.59)       | 0.22 (0.88)  | 3.99 (1.60)          | -1.57 (1.67)        |
| <i>p</i> value                                  | 0.170              | 0.370        | 0.767              | 0.805        | 0.013                | 0.346               |
| Mean change (SE) associated with ODRS = -2      | -2.91 (1.03)       | -0.47 (1.39) | -0.83 (0.78)       | -2.53 (1.16) | 4.74 (2.07)          | 1.77 (2.16)         |
| <i>p</i> value                                  | 0.005              | 0.737        | 0.284              | 0.029        | 0.022                | 0.414               |
| Mean change (SE) associated with ODRS $\leq -3$ | -4.12 (1.38)       | -2.00 (1.86) | -2.8 (0.86)        | -3.4 (1.28)  | 7.51 (2.35)          | 4.95 (2.45)         |
| <i>p</i> value                                  | 0.003              | 0.281        | 0.001              | 0.008        | 0.001                | 0.044               |

MCS = mental component summary; MSIS-29 = Multiple Sclerosis Impact Scale; ODRS = overall disability response score; PCS = physical component summary; PRO = patient-reported outcome; SF-36 = 36-Item Short Form Health Survey.

<sup>a</sup>Positive value indicates improvement; negative value indicates worsening.

<sup>b</sup>Negative value indicates improvement; positive value indicates worsening.