

**Online Appendix****Appendix Table 1:** Biomarker Standards

| <b>Biomarker (unit)</b> | <b>Manufacturer</b>                | <b>COV%</b>    | <b>LLOQ (or LOD)</b> | <b>Reporting Range</b> | <b>Matrix</b> |
|-------------------------|------------------------------------|----------------|----------------------|------------------------|---------------|
| Aldosterone (pmol/L)    | DiaSorin (Liason)                  | < 6%           | 52.90                | 52.9 – 1664.6          |               |
| TIMP-1 (ng/mL)          | R& D Systems                       | < 7%           | 0.1                  | 0.1 - 8000             | EDTA plasma   |
| MMP-2 (pg/mL)           | Meso Scale Discovery               | < 15%          | 976                  | 976 - 500,000          | Li-Hep plasma |
| MMP-9 (pg/mL)           | Meso Scale Discovery               | < 15%          | 488                  | 488 - 1,000,000        | Li-Hep plasma |
| Galectin-3 (ng/mL)      | BG Medicine                        | < 11.5%        | 1.74                 | 1.74 – 96.6            | serum         |
| sST-2 (ng/mL)           | Critical Diagnostics               | < 2.5%         | 3.13 ng/mL           | < 3.13 – 1600          | serum         |
| PINP (ug/L)             | Orion RIA                          | ≤ 10%          | 5 (LOD)              | 5 – 250                | serum         |
| PIIINP (ug/L)           | Orion RIA                          | ≤ 10%          | 1 (LOD)              | 1 – 50                 | serum         |
| NT-proBNP (pg/mL)       | Roche                              | < 2.5%         | 8                    | < 8 - 35,000           | Li-Hep plasma |
| hsTnT (ng/mL)           | Roche (5 <sup>th</sup> generation) | 14.5%<br>< 10% | 5 (LOD)<br>13 (LLOQ) | < 5 – 10,000           | EDTA plasma   |

**Abbreviations:** TIMP = tissue inhibitor of matrix metalloproteinase (MMP), PINP = n-terminal propeptide of collagen I and collagen III (PIIINP), hsTnT = high sensitivity troponin, CV = coefficient of variance, LOD = lower limit of detection (LOD), LLOQ = lower limit of quantification, EDTA = Ethylenediaminetetraacetic acid, Li Hep = lithium heparin.

**Appendix Table 2:**

| <b>Biomarker</b>   | <b>Referent Control</b>                                      | <b>Reference</b> | <b>Assay Method Antibody</b>  |
|--------------------|--|------------------|---|
| <b>Aldosterone</b> | 7-30 ng/dL (or 70-300 pg/mL)                                 | 22               | Textbook on WebMD   |
|                    | 5.31 ± 3.8 ng/dL (mean±sd) (n=2157) (or 53±38 pg/mL)         | 23               | Vitros analyzer, Ortho Clinical Diagnosis   |
|                    | 7-20 ng/dL (70-200 ng/mL) or 0.2-0.8 nmol/L (200-800 pmol/L) | 24               | ACP Lab Reference Ranges  |
| <b>sST-2</b>       | 20 (17, 26) ng/mL (median/iqr)                               | 8                | Presage immunoassay, Critical Diagnostics, San Diego                              |
| <b>Galectin-3</b>  | 12 (9, 15) ng/mL (median/iqr)                                | 8                | Enzyme-linked immunosorbent assay, BG Medicine, Waltham, MA                       |
| <b>MMP-2</b>       | 339.7 ± 9.3 ng/mL (mean±sem) (n=241)                         | 7                | Multiplex suspension array, MMP Base kit LMP000, BioPlex 200, BioRad Laboratories |
|                    | 374.8 ± 35.7 ng/mL (mean±sem) (n=15)                         | 14               | Multiplex suspension array, MMP Base kit LMP000, BioPlex 200, BioRad Laboratories |
|                    | 236.6 (217.6,275.3) ug/L (median/iqr) (n=49)                 | 18               | R&D Systems   |
|                    | 335 (323, 443) ng/mL (median/iqr)                            | 8                | Immunoassay (R&D Systems, Minneapolis, MN)  |
| <b>MMP-9</b>       | 95.0 ± 3.8 ng/mL (mean±sem) (n=241)                          | 7                | Multiplex suspension array, MMP Base kit LMP000, BioPlex 200, BioRad Laboratories |
|                    | 121.1 ± 13.1 ng/mL (mean±sem) (n=15)                         | 14               | Multiplex suspension array, MMP Base kit LMP000, BioPlex 200, BioRad Laboratories |
|                    | 58.8 (38.0,134.4) ug/L (median/iqr) (n=49)                   | 18               | R&D Systems   |
|                    | 145 ± 88 ug/L (mean±sd) (n=9)                                | 19               | ELISA, R&D Systems  |
| <b>TIMP-1</b>      | 72.2 ± 1.4 ng/mL (mean±sem) (n=241)                          | 7                | Multiplex suspension array, TIMP MSA kit LKT003, BioPlex 200, BioRad Laboratories |
|                    | 106.3 ± 4.4 ng/mL (mean±sem) (n=15)                          | 14               | Multiplex suspension array, TIMP MSA kit LKT003, BioPlex 200, BioRad Laboratories |
|                    | 827.7 ± 111.5 ug/L (mean±sd) (n=92)                          | 15               | ELISA (Amersham Pharmacia Biotech, UK)  |
|                    | 217.2 (203.3,245.2) ug/L (median/iqr) (n=49)                 | 18               | R&D Systems   |
|                    | 165 ± 67 ug/L (mean±sd) (n=9)                                | 19               | ELISA, R&D Systems  |
|                    | 634 ± 7 ng/mL (mean±sem)                                     | 20               | GE Healthcare Life Sciences   |
| <b>PINP</b>        | 37.1 ± 1.3 ng/mL (mean±sem) (n=241)                          | 7                | Radioimmunoassay  |
|                    | 46.6 ± 19.1 ug/L (mean±sd) (n=92)                            | 15               | Radioimmunoassay, Orion Diagnostica   |
|                    | 53.4 ± 25.9 ug/L (mean±sd) (n=25)                            | 17               | Radioimmunoassay, Abbott  |
|                    | 39.6 ± 17.4 ug/L (mean±sd) (n=9)                             | 19               | Radioimmunoassay, Abbott  |

|               |  |    |                                      |
|---------------|--|----|--------------------------------------|
| <b>PIIINP</b> | 7.2 ± 0.1 ng/mL (mean±sem) (n=241)       | 7  | Radioimmunoassay                     |
|               | 3.5 ± 1.3 ug/L (mean±sd) (n=92)          | 15 | Radioimmunoassay, Orion Diagnostica  |
|               | 3.1 (2.4,4.0) ng/mL (median/iqr) (n=283) | 16 | Radioimmunoassay, Orion Diagnostica  |
|               | 4.4 ± 1.1 ug/L (mean±sd) (n=25)          | 17 | Radioimmunoassay, Abbott             |
|               | 5.8 (4.4 ,7.0) ug/L (median/iqr) (n=49)  | 18 | Radioimmunoassay, Orion Diagnostica  |
|               | 6.5 (6.1, 8.2) ng/mL (median/iqr)        | 8  | Quest Diagnostics, Valencia, CA      |
|               | 4.1 ± 0.7 ug/L (mean±sd) (n=9)           | 19 | Radioimmunoassay, Abbott             |
|               | 457 (175-1160) pg/mL (median/iqr)        | 20 | MyBioSource, San Diego               |
|               | 3.4 ± 0.2 ug/L (mean±sem) (n=30)         | 21 | Radioimmunoassay, Farnos Diagnostica |

Abbreviations: TIMP = tissue inhibitor of matrix metalloproteinase (MMP), PINP = n-terminal propeptide of collagen I and collagen III (PIIINP),

Median (IQR) referent control data for PIIINP and MMP-2 were taken from a previously published study in which 241 subjects of age, sex, and race distribution similar to this study population were examined (7). However, these well-characterized subjects had no clinical, serological, or cardiac structural/functional abnormalities as evidenced by a normal echocardiography and 6-minute hall walk distance. Median (IQR) referent control data for Gal-3 were taken from a previously published study in which 1092 subjects of age, sex, and race distribution similar to this study population were examined (25). Median (IQR) referent control data for sST-2 were aggregated from previously published studies (including the Framingham study) in which subjects of age, sex, and race distribution similar to this study population were examined (26-29). Reported normal values for sST-2 were 20 ng/mL (95% CI of 17-26 ng/mL), and for Gal-3 was 12 ng/mL (95% CI of 9-15 ng/mL) (8). Although small differences between men and women have been seen in the biomarkers described above, because the populations of both this study and the referent control populations have similar sex distribution, the referent control values listed in Appendix Table 2 represent the total referent population examined.

**Appendix Table 3: Relationship Between Profibrotic Biomarker and Outcome: Independent effect of each Biomarker**

| Marker                       | <b>Baseline levels vs outcomes</b><br><b>HR (95% CI), p-value log transformed per SD</b> |                             |
|------------------------------|--|-----------------------------|
|                              | <b>Primary outcome*</b>  | <b>CV Death*</b>            |
| <b>Aldo</b><br>(pmol/L)      | 0.89 (0.78-1.01)<br>p=0.07   | 0.91 (0.76-1.09)<br>p=0.30  |
| <b>sST2</b><br>(ng/mL)       | 1.11 (0.98-1.25)<br>p=0.09   | 1.08 (0.91-1.29)<br>p=0.37  |
| <b>TIMP-1</b><br>(ng/mL)     | 1.20 (1.03-1.38)<br>p=0.017  | 1.43 (1.14-1.79)<br>p=0.002 |
| <b>MMP-2</b><br>(ng/mL)      | 1.02 (0.90-1.16)<br>p=0.74   | 1.00 (0.83-1.20)<br>p=0.99  |
| <b>MMP-9</b><br>(ng/mL)      | 1.02 (0.91-1.14)<br>p=0.74   | 1.01 (0.85-1.20)<br>p=0.93  |
| <b>Galectin-3</b><br>(ng/mL) | 1.08 (0.95-1.23)<br>p=0.26   | 1.04 (0.86-1.26)<br>p=0.67  |
| <b>PINP</b><br>(ng/mL)       | 0.90 (0.77-1.04)<br>p=0.16   | 0.89 (0.72-1.11)<br>p=0.32  |
| <b>PIIINP</b><br>(ng/mL)     | 1.07 (0.91-1.25)<br>p=0.44   | 1.14 (0.90-1.44)<br>p=0.29  |

Abbreviations: \*adjusted for treatment + baseline covariates (including BNP, NT-proBNP, hsTnT) + all 8 profibrotic biomarkers,

TIMP = tissue inhibitor of matrix metalloproteinase (MMP), PINP = n-terminal propeptide of collagen I and collagen III (PIIINP),

**Appendix Table 4: Compare c-statistic to determine if fibrosis biomarkers added independent value to prognosis.**

| (treatment included in all)   | Primary Outcome        | CV Death               |
|---|------------------------|------------------------|
| <b>M1:</b> Baseline Covariates  | 0.66                   | 0.67                   |
| <b>M2:</b> M1 + BNP, NT-proBNP, hsTnT   | 0.71                   | 0.70                   |
| <b>M3:</b> M2 + TIMP-1  | 0.72<br>(p=0.08 vs M2) | 0.71<br>(p=0.37 vs M2) |
| <b>M4:</b> M2 + all 8 profibrotic biomarkers  | 0.72                   | 0.72                   |
| <b>M5:</b> BNP, NT-proBNP, hsTnT + all 8 profibrotic biomarkers<br>(i.e. M4 minus M1) | 0.70                   | 0.68                   |

Abbreviations: BNP = b-type natriuretic peptide, NTproBNP = n-terminal pro BNP, TIMP = tissue inhibitor of matrix metalloproteinase (MMP), PINP = n-terminal propeptide of collagen I and collagen III (PIINP),

**Appendix Table 5: Baseline Demographics**

| Patients in Paradigm-HF with biomarker vs no biomarker data | <b>No Baseline Biomarkers</b> | <b>Baseline Biomarkers</b> |                |
|---|-------------------------------|----------------------------|----------------|
|   | <b>n=6332</b>                 | <b>n=2067</b>              | <b>p-value</b> |
| <b>Age (years)</b>  | 63 ± 12                       | 67 ± 10                    | <0.001         |
| <b>Female sex</b>   | 1446 (23 %)                   | 386 (19 %)                 | <0.001         |
| <b>Body Mass Index</b>                                      | 27.7 ± 5.5                    | 29.5 ± 5.4                 | <0.001         |
| <b>NYHA Class</b>   |                               |                            | <0.001         |
| <b>1</b>  | 342 (5 %)                     | 47 (2 %)                   |                |
| <b>2</b>  | 4410 (70 %)                   | 1509 (73 %)                |                |
| <b>3</b>  | 1520 (24 %)                   | 498 (24 %)                 |                |
| <b>4</b>  | 49 (1 %)                      | 11 (1 %)                   |                |
| <b>LV Ejection Fraction</b>                                 | 29 ± 6                        | 30 ± 6                     | <0.001         |
| <b>Prior use of ACEi</b>                                    | 4865 (77 %)                   | 1667 (81 %)                | <0.001         |
| <b>Prior use of ARB</b>                                     | 1478 (23 %)                   | 414 (20 %)                 | 0.002          |
| <b>Prior HF hospitalization</b>                             | 4035 (64 %)                   | 1239 (60 %)                | 0.001          |
| <b>Hypertension status</b>                                  | 4333 (68 %)                   | 1607 (78 %)                | <0.001         |
| <b>Race</b>   |                               |                            | <0.001         |
| <b>White</b>  | 3582 (57 %)                   | 1962 (95 %)                |                |
| <b>Black</b>  | 364 (6 %)                     | 64 (3 %)                   |                |
| <b>Asian</b>  | 1501 (24 %)                   | 8 (0 %)                    |                |

|                                    |             |             |        |
|------------------------------------|-------------|-------------|--------|
| <b>Other</b>                       | 885 (14 %)  | 33 (2 %)    |        |
| <b>Region</b>                      |             |             | <0.001 |
| <b>North America</b>               | 265 (4 %)   | 337 (16 %)  |        |
| <b>Latin America</b>               | 1433 (23 %) | 0 (0 %)     |        |
| <b>Western Europe and Other</b>    | 1112 (18 %) | 939 (45 %)  |        |
| <b>Central/Eastern Europe</b>      | 2035 (32 %) | 791 (38 %)  |        |
| <b>Asia-Pacific</b>                | 1487 (23 %) | 0 (0 %)     |        |
| <b>Systolic Blood Pressure</b>     | 121 ± 15    | 123 ± 16    | <0.001 |
| <b>Diabetes Mellitus</b>           | 2089 (33 %) | 818 (40 %)  | <0.001 |
| <b>Heart Rate</b>                  | 73 ± 12     | 71 ± 12     | <0.001 |
| <b>Ischemic Cardiomyopathy</b>     | 3711 (59 %) | 1325 (64 %) | <0.001 |
| <b>Prior Myocardial Infarction</b> | 2628 (42 %) | 1006 (49 %) | <0.001 |
| <b>Prior Atrial Fibrillation</b>   | 2091 (33 %) | 1000 (48 %) | <0.001 |
| <b>Prior Stroke</b>                | 515 (8 %)   | 210 (10 %)  | 0.004  |
| <b>ICD</b>                         | 656 (10 %)  | 587 (28 %)  | <0.001 |
| <b>CRT</b>                         | 345 (5 %)   | 229 (11 %)  | <0.001 |
| <b>Diuretic</b>                    | 5045 (80 %) | 1693 (82 %) | 0.027  |
| <b>Beta Blockers</b>               | 5841 (92 %) | 1970 (95 %) | <0.001 |
| <b>Digoxin</b>                     | 2074 (33 %) | 465 (22 %)  | <0.001 |
| <b>Aldosterone</b>                 | 3740 (59 %) | 931 (45 %)  | <0.001 |
| <b>Baseline Creatinine</b>         | 1.1 ± 0.3   | 1.2 ± 0.3   | <0.001 |

|                                  |                   |                   |        |
|----------------------------------|-------------------|-------------------|--------|
| <b>Baseline BNP (pg/ml)</b>      | 261 [154 , 496 ]  | 229 [154 , 400 ]  | <0.001 |
| <b>Baseline NTproBNP (pg/ml)</b> | 1665 [903 , 3385] | 1485 [852 , 2907] | <0.001 |
| <b>hs-troponin T (ng/L)</b>      | 24 [17, 31]       | 16 [11, 25]       | 0.40   |

Abbreviations: ICD = implantable cardiac defibrillator, CRT = cardiac resynchronization therapy, LV = left ventricular, HF = heart failure, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = b-type natriuretic peptide, NTproBNP = n-terminal pro BNP, NYHA = New York heart association



**Appendix Table 6: Baseline Demographics**

| Patients from full Paradigm-HF cohort vs those with baseline biomarkers vs those with both baseline and follow-up biomarkers | <b>PARADIGM-HF cohort</b> | <b>Baseline Biomarkers</b> | <b>Full cohort vs Baseline biomarker cohort</b> | <b>Baseline + follow-up biomarkers</b> | <b>Baseline only vs Baseline + follow-up</b> |
|--|---------------------------|----------------------------|---|--|--|
|  | <b>n=8399</b>             | <b>n=2067</b>              | <b>p-value</b>                                  | <b>n=1776</b>                          | <b>p-value</b>                               |
| <b>Age (years)</b>   | 64 ± 11                   | 67 ± 10                    | <0.001  | 67 ± 10                                | 0.027  |
| <b>Female sex</b>  | 1832 (22 %)               | 386 (19 %)                 | <0.001  | 332 (19 %)                             | 0.96   |
| <b>Body Mass Index</b>   | 28.2 ± 5.5                | 29.5 ± 5.4                 | <0.001  | 29.6 ± 5.5                             | 0.005  |
| <b>NYHA Class</b>  |                           |                            | <0.001  |  | 0.021  |
| <b>1</b>   | 389 (5 %)                 | 47 (2 %)                   |   | 40 (2 %)                               |  |
| <b>2</b>   | 5919 (71 %)               | 1509 (73 %)                |   | 1317 (74 %)                            |  |
| <b>3</b>   | 2018 (24 %)               | 498 (24 %)                 |   | 407 (23 %)                             |  |
| <b>4</b>   | 60 (1 %)                  | 11 (1 %)                   |   | 10 (1 %)                               |  |
| <b>LV Ejection Fraction</b>  | 29 ± 6                    | 30 ± 6                     | <0.001  | 31 ± 6                                 | 0.001  |
| <b>Prior use of ACEi</b>   | 6532 (78 %)               | 1667 (81 %)                | <0.001  | 1427 (80 %)                            | 0.39   |
| <b>Prior use of ARB</b>  | 1892 (23 %)               | 414 (20 %)                 | 0.002   | 363 (20 %)                             | 0.25   |
| <b>Prior HF hospitalization</b>  | 5274 (63 %)               | 1239 (60 %)                | 0.001   | 1047 (59 %)                            | 0.023  |
| <b>Hypertension status</b>   | 5940 (71 %)               | 1607 (78 %)                | <0.001  | 1372 (77 %)                            | 0.18   |
| <b>Race</b>  |                           |                            | <0.001  |  | <0.001                                       |
| <b>White</b>   | 5544 (66 %)               | 1962 (95 %)                |   | 1700 (96 %)                            |  |
| <b>Black</b>   | 428 (5 %)                 | 64 (3 %)                   |   | 44 (2 %)                               |  |
| <b>Asian</b>   | 1509 (18 %)               | 8 (0 %)                    |   | 6 (0 %)                                |  |
| <b>Other</b>   | 918 (11 %)                | 33 (2 %)                   |   | 26 (1 %)                               |  |

|                                    |                   |                   |        |                   |        |
|------------------------------------|-------------------|-------------------|--------|-------------------|--------|
| <b>Region</b>                      |                   |                   | <0.001 |                   | 0.016  |
| <b>North America</b>               | 602 (7 %)         | 337 (16 %)        |        | 276 (16 %)        |        |
| <b>Latin America</b>               | 1433 (17 %)       | 0 (0 %)           |        | 0 (0 %)           |        |
| <b>Western Europe and Other</b>    | 2051 (24 %)       | 939 (45 %)        |        | 802 (45 %)        |        |
| <b>Central Europe</b>              | 2826 (34 %)       | 791 (38 %)        |        | 698 (39 %)        |        |
| <b>Asia-Pacific</b>                | 1487 (18 %)       | 0 (0 %)           |        | 0 (0 %)           |        |
| <b>Systolic Blood Pressure</b>     | 121 ± 15          | 123 ± 16          | <0.001 | 123 ± 16          | 0.21   |
| <b>Diabetes Mellitus</b>           | 2907 (35 %)       | 818 (40 %)        | <0.001 | 705 (40 %)        | 0.78   |
| <b>Heart Rate</b>                  | 72 ± 12           | 71 ± 12           | <0.001 | 71 ± 12           | 0.08   |
| <b>Ischaemic Cardiomyopathy</b>    | 5036 (60 %)       | 1325 (64 %)       | <0.001 | 1139 (64 %)       | 0.94   |
| <b>Prior Myocardial Infarction</b> | 3634 (43 %)       | 1006 (49 %)       | <0.001 | 866 (49 %)        | 0.84   |
| <b>Prior Atrial Fibrillation</b>   | 3091 (37 %)       | 1000 (48 %)       | <0.001 | 864 (49 %)        | 0.54   |
| <b>Prior Stroke</b>                | 725 (9 %)         | 210 (10 %)        | 0.004  | 178 (10 %)        | 0.61   |
| <b>ICD</b>                         | 1243 (15 %)       | 587 (28 %)        | <0.001 | 498 (28 %)        | 0.37   |
| <b>CRT</b>                         | 574 (7 %)         | 229 (11 %)        | <0.001 | 190 (11 %)        | 0.17   |
| <b>Diuretic</b>                    | 6738 (80 %)       | 1693 (82 %)       | 0.027  | 1444 (81 %)       | 0.08   |
| <b>Beta Blockers</b>               | 7811 (93 %)       | 1970 (95 %)       | <0.001 | 1695 (95 %)       | 0.48   |
| <b>Digoxin</b>                     | 2539 (30 %)       | 465 (22 %)        | <0.001 | 394 (22 %)        | 0.40   |
| <b>Aldosterone</b>                 | 4671 (56 %)       | 931 (45 %)        | <0.001 | 798 (45 %)        | 0.81   |
| <b>Baseline Creatinine</b>         | 1.1 ± 0.3         | 1.2 ± 0.3         | <0.001 | 1.2 ± 0.3         | <0.001 |
| <b>Baseline BNP (pg/ml)</b>        | 253 [154 , 468 ]  | 229 [154 , 400 ]  | <0.001 | 221 [149 , 384 ]  | <0.001 |
| <b>Baseline NTproBNP (pg/ml)</b>   | 1612 [886 , 3224] | 1485 [852 , 2907] | <0.001 | 1444 [827 , 2788] | <0.001 |
| <b>hs-troponin T (ng/L)</b>        | 17 [11, 25]       | 16 [11, 25]       | 0.40   | 16 [10, 24]       | <0.001 |

Abbreviations: ICD = implantable cardiac defibrillator, CRT = cardiac resynchronization therapy, LV = left ventricular, HF = heart failure, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BNP = b-type natriuretic peptide, NTproBNP = n-terminal pro BNP, NYHA = New York heart association

**Appendix Table 7: Effects of sacubitril/valsartan on profibrotic biomarkers adjusted for systolic blood pressure**

| Marker            | Visit       | Baseline to 8 Mo change: |                          |  |          |  |           |
|-------------------|-------------|--------------------------|--------------------------|--|----------|--|-----------|
|                   |             | Enalapril                | Sacubitril/<br>valsartan | *Adjusted for baseline biomarker<br>Sacubitril/<br>valsartan effect* | P-value* | ** Additionally adjusted for<br>baseline SBP + SBP change<br>Sacubitril/<br>valsartan effect** | P-value** |
| Aldo<br>(pmol/L)  | IQR         | [-34%, +26%]             | [-37%, +21%]             |  | --       |  |           |
|                   | %<br>change | -10.3%                   | -14.2%                   | -6% (-11%, -1%)  | 0.020    | -7% (-12%, -2%)  | 0.007     |
| sST2<br>(ng/ml)   | IQR         | [-14%, +18%]             | [-18%, +10%]             |  | --       |  | --        |
|                   | %<br>change | +0.8%                    | -5.5%                    | -7% (-9%, -4%)   | <0.001   | -6% (-9%, -4%)   | <0.001    |
| TIMP-1<br>(ng/ml) | IQR         | [-11%, +15%]             | [-15%, +10%]             |  | --       |  | --        |
|                   | %<br>change | +0.3%                    | -3.6%                    | -4% (-7%, -1%)   | 0.003    | -5% (-7%, -2%)   | 0.001     |
| MMP-2             | IQR         | [-10%, +7.6%]            | [-11%, +7.4%]            |  |          |  |           |
|                   | %<br>change | -0.8%                    | -2.1%                    | -1% (-4%, +1%)   | 0.36     | -1% (-4%, +2%)   | 0.46      |
| MMP-9             | IQR         | [-37%, +54%]             | [-43%, +47%]             |  |          |  |           |
|                   | %<br>change | -3.0%                    | -10.5%                   | -8% (-14%, -2%)  | 0.010    | -9% (-15%, -3%)  | 0.006     |
| Gal-3             | IQR         | [-7.4%, +23%]            | [-8.6%, +21%]            |  |          |  |           |
|                   | %<br>change | +5.3%                    | +4.7%                    | -1% (-3%, +2%)   | 0.51     | -1% (-4%, +1%)   | 0.24      |
| PINP              | IQR         | [-20%, +26%]             | [-26%, +18%]             |  |          |  |           |
|                   | %<br>change | +0.6%                    | -6.2%                    | -6% (-10%, -3%)  | <0.001   | -6% (-10%, -3%)  | <0.001    |
| PIIINP            | IQR         | [-22%, +22%]             | [-22%, +18%]             |  |          |  |           |
|                   | %<br>change | -1.7%                    | -4.5%                    | -3% (-6%, 0%)  | 0.086    | -3% (-6%, 0%)  | 0.090     |