

| Diagnostic tool      | Acute clinical flare<br>CAI>4 | clinical remission<br>CAI≥2 and ≤4 | sustained clinical<br>remission<br>CAI<2 | p-value from<br>Mann<br>Whitney U |
|----------------------|-------------------------------|------------------------------------|------------------------------------------|-----------------------------------|
| median ± STD         | N = 52                        | N = 119                            | N = 358                                  |                                   |
| Lactoferrin          | 33.1 (0.1 – 145.0)            | 20.0 (0.1 – 167.6)                 |                                          | 0.109                             |
|                      | 33.1 (0.1 – 145.0)            |                                    | 3.6 (0.0 – 160.7)                        | <b>&lt; 0.000</b>                 |
|                      |                               | 20.0 (0.1 – 167.6)                 | 3.6 (0.0 – 160.7)                        | <b>&lt; 0.000</b>                 |
| Calprotectin         | 25.0 (1.7 – 105.6)            | 19.2 (0.01 – 365.5)                |                                          | 0.057                             |
|                      | 25.0 (1.7 – 105.6)            |                                    | 9.2 (0.01 – 369.3)                       | <b>&lt; 0.000</b>                 |
|                      |                               | 19.2 (0.01 – 365.5)                | 9.2 (0.01 – 369.3)                       | <b>0.004</b>                      |
| PMN-elastase         | 0.06 (0.0 – 0.4)              | 0.04 (0.0 – 0.4)                   |                                          | <b>0.034</b>                      |
|                      | 0.06 (0.0 – 0.4)              |                                    | 0.02 (0.0 – 0.7)                         | <b>&lt; 0.000</b>                 |
|                      |                               | 0.04 (0.0 – 0.4)                   | 0.02 (0.0 – 0.7)                         | <b>0.022</b>                      |
| CRP                  | 0.5 (0.1 – 10.6)              | 0.2 (0.1 – 9.9)                    |                                          | 0.051                             |
|                      | 0.5 (0.1 – 10.6)              |                                    | 0.2 (0.0 – 3.0)                          | <b>&lt; 0.000</b>                 |
|                      |                               | 0.2 (0.1 – 9.9)                    | 0.2 (0.0 – 3.0)                          | <b>0.004</b>                      |
| White blood<br>count | 7.3 (3.0 – 14.7)              | 6.6 (2.7 – 13.7)                   |                                          | <b>0.011</b>                      |
|                      | 7.3 (3.0 – 14.7)              |                                    | 6.3 (3.1 – 14.9)                         | <b>&lt; 0.000</b>                 |
|                      |                               | 6.6 (2.7 – 13.7)                   | 6.3 (3.1 – 14.9)                         | 0.054                             |

| Diagnostic tool<br>median (range) | clinically active<br>intestinal<br>inflammation<br>N = 35 | in clinical remission<br>intestinal inflammation<br>N = 37 | Mucosal healing<br>N = 107 | p-value from<br>Mann<br>Whitney U<br>test |
|-----------------------------------|-----------------------------------------------------------|------------------------------------------------------------|----------------------------|-------------------------------------------|
| Lactoferrin                       | 43.7 (0.1 – 145.0)                                        | 36.7 (0.2 – 160.7)                                         |                            | 0.687                                     |
|                                   | 43.7 (0.1 – 145.0)                                        |                                                            | 4.4 (0.0 – 126.9)          | <b>&lt; 0.000</b>                         |
|                                   |                                                           | 36.7 (0.2 – 160.7)                                         | 4.4 (0.0 – 126.9)          | <b>&lt; 0.000</b>                         |
| Calprotectin                      | 25.0 (1.7 – 105.6)                                        | 19.8 (1.4 – 98.5)                                          |                            | 0.292                                     |
|                                   | 25.0 (1.7 – 105.6)                                        |                                                            | 10.4 (0.01 – 62.1)         | <b>&lt; 0.000</b>                         |
|                                   |                                                           | 19.8 (1.4 – 98.5)                                          | 10.4 (0.01 – 62.1)         | <b>0.003</b>                              |
| PMN-elastase                      | 0.06 (0.0 – 0.4)                                          | 0.03 (0.0 – 0.4)                                           |                            | 0.052                                     |
|                                   | 0.06 (0.0 – 0.4)                                          |                                                            | 0.02 (0.0 – 0.7)           | <b>&lt; 0.000</b>                         |
|                                   |                                                           | 0.03 (0.0 – 0.4)                                           | 0.02 (0.0 – 0.7)           | <b>&lt; 0.011</b>                         |
| CRP                               | 0.7 (0.1 – 10.6)                                          | 0.2 (0.2 – 9.9)                                            |                            | <b>0.011</b>                              |
|                                   | 0.7 (0.1 – 10.6)                                          |                                                            | 0.2 (0.0 – 2.8)            | <b>&lt; 0.000</b>                         |
|                                   |                                                           | 0.2 (0.2 – 9.9)                                            | 0.2 (0.0 – 2.8)            | 0.243                                     |
| White blood<br>count              | 7.0 (3.0 – 14.7)                                          | 6.5 (3.7 – 13.0)                                           |                            | 0.098                                     |
|                                   | 7.0 (3.0 – 14.7)                                          |                                                            | 6.4 (3.8 – 13.0)           | <b>0.036</b>                              |
|                                   |                                                           | 6.5 (3.7 – 13.0)                                           | 6.4 (3.8 – 13.0)           | 0.793                                     |

**Table 2:** Sensitivity and specificity, PPV and NPV for the five diagnostic biomarkers compared to sustained clinical remission (**CAI < 2, normal bowel frequency and no blood in stool**) as gold standard

| Diagnostic tool   |         | sensitivity<br>in % | specificity<br>in % | PPV<br>in % | NPV<br>in % |
|-------------------|---------|---------------------|---------------------|-------------|-------------|
| Lactoferrin       | n = 515 | 63                  | 63                  | 54          | 70          |
| Calprotectin 50   | n = 515 | 8                   | 98                  | 75          | 60          |
| PMN-elastase      | n = 515 | 34                  | 86                  | 63          | 64          |
| CRP               | n = 526 | 32                  | 87                  | 66          | 83          |
| white blood count | n = 529 | 23                  | 90                  | 63          | 61          |

**Table 4:** Sensitivity and specificity, PPV and NPV for the five diagnostic biomarkers compared to mucosal healing using **endoscopy as gold standard**

| Diagnostic tool   |         | sensitivity<br>in % | specificity<br>in % | PPV<br>in % | NPV<br>in % |
|-------------------|---------|---------------------|---------------------|-------------|-------------|
| Lactoferrin       | n = 174 | 75                  | 63                  | 57          | 80          |
| Calprotectin 50   | n = 174 | 10                  | 99                  | 88          | 63          |
| PMN-elastase      | n = 174 | 32                  | 87                  | 61          | 66          |
| CRP               | n = 176 | 46                  | 83                  | 64          | 70          |
| white blood count | n = 179 | 23                  | 89                  | 57          | 64          |

**Table 5:** Sensitivity and specificity, area under the curve and p- value for ROC analyses, relative risk with elevated biomarkers at baseline to develop a flare within the study.

| Diagnostic tool   |         | Cut-off | AUC (95% CI)          | sensitivity<br>in % | specificity<br>in % | Diagnostic<br>accuracy<br>In % | p-value | RR (95% CI), p-value                      |
|-------------------|---------|---------|-----------------------|---------------------|---------------------|--------------------------------|---------|-------------------------------------------|
| Lactoferrin       | n = 161 | 11.9    | 0.734 (0.654 – 0.813) | 70.3                | 70.1                | 70.2                           | < 0.000 | <b>1.99 (1.47 – 2.71),<br/>p&lt;0.001</b> |
| Calprotectin 50   | n = 161 | 13.9    | 0.700 0.619 – 0.782)  | 64.1                | 63.9                | 64.0                           | < 0.000 | <b>1.58 (1.20 – 2.09),<br/>p=0.001</b>    |
| PMN-elastase      | n = 163 | 0.035   | 0.697 (0.614 – 0.780) | 54.7                | 73.2                | 64.0                           | < 0.000 | <b>1.67 (1.21 – 2.29)<br/>p&lt;0.001</b>  |
| CRP               | n = 151 | 0.25    | 0.651 (0.562 – 0.740  | 62.1                | 62.9                | 62.5                           | 0.001   | <b>1.52 (1.15 – 2.0)<br/>p=0.002</b>      |
| White blood count | n = 166 | n.s.    | 0.569 (0.477 – 0.660) | n.s                 | n.s                 |                                | 0.133   |                                           |