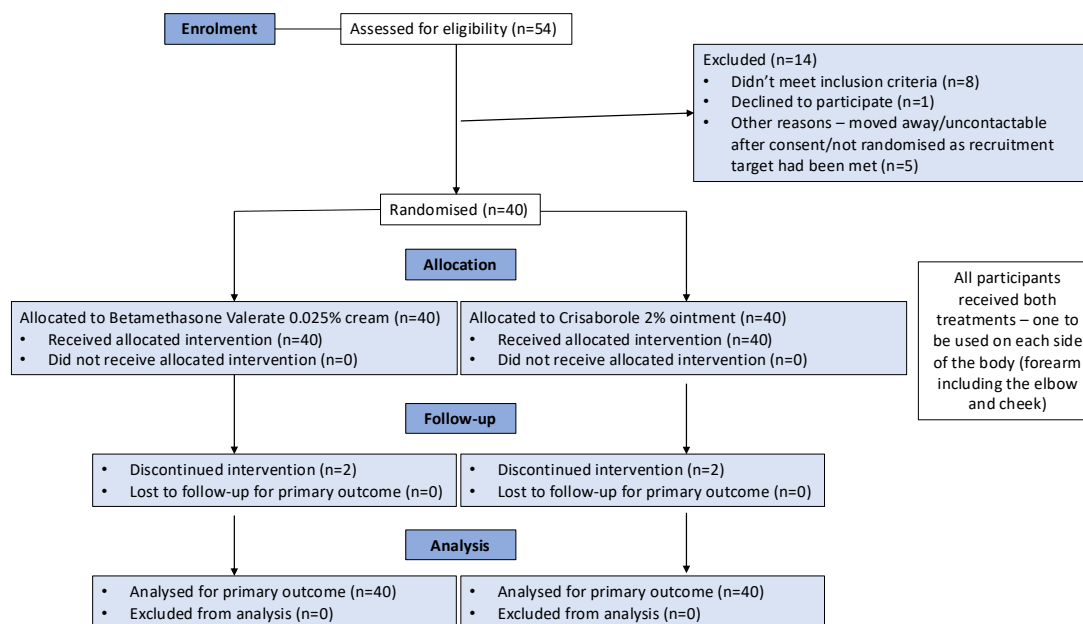


## Participant flow



Validation of a novel composite of skin biomarkers as a primary outcome measure for evaluating the safety of treatments for atopic dermatitis study 2: a randomised controlled trial (phase 2) comparing the effects of crisaborole 2% ointment (CRBo) to betamethasone valerate 0.025% cream (BMVc) on skin structure and function in participants with atopic dermatitis [SMART2]

ISRCTN52806782

## Baseline characteristics

| Metric                                                                                          | Participants receiving both BMVc and CRBo (N=40) |
|-------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Age (years)                                                                                     | 33.2 ±11.91                                      |
| Sex as assigned at birth (Female)                                                               | 21 (53)                                          |
| Ethnicity:                                                                                      |                                                  |
| English/Welsh/Scottish/ Northern Irish/British                                                  | 27 (68)                                          |
| Any other white background                                                                      | 1 (3)                                            |
| Indian                                                                                          | 2 (5)                                            |
| Pakistani                                                                                       | 2 (5)                                            |
| Chinese                                                                                         | 1 (3)                                            |
| Any other Asian background                                                                      | 1 (3)                                            |
| White & black Caribbean                                                                         | 1 (3)                                            |
| Any other mixed/multiple ethnic background                                                      | 1 (3)                                            |
| Caribbean                                                                                       | 1 (3)                                            |
| Arab                                                                                            | 1 (3)                                            |
| Prefer not to say                                                                               | 0 (0)                                            |
| Fitzpatrick skin type:                                                                          |                                                  |
| Very fair (1)                                                                                   | 4 (10)                                           |
| Fair (2)                                                                                        | 13 (33)                                          |
| Medium (3)                                                                                      | 13 (33)                                          |
| Olive (4)                                                                                       | 6 (15)                                           |
| Brown (5)                                                                                       | 4 (10)                                           |
| Does the participant meet the UK Working Party Diagnostic Criteria for Atopic Dermatitis? (Yes) | 40 (100)                                         |
| Epidermal thickness (µm)                                                                        |                                                  |
| <i>Volar forearm</i>                                                                            | 88.9 ±11.90                                      |
| <i>Antecubital fossa</i>                                                                        | 91.7 ±24.40                                      |
| <i>Cheek</i>                                                                                    | 82.5 ±11.10                                      |
| Superficial plexus depth (µm)                                                                   |                                                  |
| <i>Volar forearm</i>                                                                            | 123 ±11.40                                       |
| <i>Antecubital fossa</i>                                                                        | 117 ±20.90                                       |
| <i>Cheek</i>                                                                                    | 110 ±10.20                                       |
| Mexameter (AU)                                                                                  |                                                  |
| <i>Volar forearm</i>                                                                            | 230 ±76.60                                       |
| <i>Antecubital fossa</i>                                                                        | 297 ±71.90                                       |
| <i>Cheek</i>                                                                                    | 365 ±116.0                                       |
| TEWL (g/m <sup>2</sup> /h) <sup>1</sup>                                                         |                                                  |
| <i>Volar forearm</i>                                                                            | 13.7 ±3.12                                       |
| <i>Antecubital fossa</i>                                                                        | 18.2 ±7.60                                       |
| <i>Cheek</i>                                                                                    | 22.0 ±5.86                                       |
| TEWL <sub>20</sub> (g/m <sup>2</sup> /h) <sup>2</sup>                                           | 44.0 ±17.90                                      |

<sup>1</sup>Transepidermal water loss, <sup>2</sup>measured on the forearm only; ±SD; (%)

## Outcome measures

| Outcome measure                                                                                                                                        | Timepoint                                                      | Treatment mean (95% CI)                                               |                                                                        | Δ(CRBo - BMVc)                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------|
| Primary                                                                                                                                                |                                                                | CRBo                                                                  | BMVc                                                                   | Mean (95% CI)                                                    |
| The difference in the change in <b>epidermal thickness</b> (μm) on the volar forearm measured by OCT                                                   | Baseline to day 29                                             | -2.76 (-5.61,0.10)                                                    | -9.07 (-11.93,-6.21)                                                   | 6.32 (3.45,9.18)                                                 |
| Secondary                                                                                                                                              |                                                                |                                                                       |                                                                        |                                                                  |
| 1. The difference in the change in <b>epidermal thickness</b> (μm) on the antecubital fossa measured by OCT                                            | Baseline to day 29                                             | -9.12 (-13.05,-5.19)                                                  | -23.82 (-27.75,-19.88)                                                 | 14.69 (11.03,18.35)                                              |
| 2. The difference in the change in <b>epidermal thickness</b> (μm) on the cheek measured by OCT                                                        | Baseline to day 15                                             | -7.41 (-9.93,-4.88)                                                   | -9.28 (-11.81,-6.75)                                                   | 1.87 (-0.85,4.60)                                                |
| 3a. The difference in the change in <b>superficial plexus depth</b> (μm) on the volar forearm measured by OCT                                          | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | -4.05 (-8.38,0.29)<br>-1.61 (-6.07,2.85)<br>-2.99 (-8.01,2.02)        | -11.86 (-16.19,-7.52)<br>-9.27 (-13.73,-4.82)<br>-0.68 (-5.69,4.34)    | 7.81 (3.10,12.52)<br>7.66 (2.79,12.53)<br>-2.32 (-7.89,3.26)     |
| 3b. The difference in the change in <b>superficial plexus depth</b> (μm) on the antecubital fossa measured by OCT                                      | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | -9.32 (-13.19,-5.44)<br>-0.17 (-5.50,5.15)<br>2.71 (-2.64,8.05)       | -15.50 (-19.38,-11.63)<br>-16.38 (-21.70,-11.05)<br>-2.86 (-8.21,2.49) | 6.19 (1.52,10.85)<br>16.20 (9.42,22.99)<br>5.57 (-1.22,12.36)    |
| 3c. The difference in the change in <b>superficial plexus depth</b> (μm) on the cheek measured by OCT                                                  | Baseline to day 15<br>Baseline to day 57                       | -1.39 (-4.56,1.78)<br>-3.01 (-7.09,1.07)                              | -4.40 (-7.57,-1.23)<br>-1.20 (-5.28,2.88)                              | 3.01 (-0.47,6.49)<br>-1.81 (-6.44,2.82)                          |
| 4a. The difference in the change in <b>objective redness</b> (AU) on the volar forearm measured by mexameter                                           | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | -15.05 (-29.64,-0.46)<br>-15.30 (-30.37,-0.23)<br>1.79 (-11.94,15.52) | -30.47 (-45.06,-15.88)<br>-23.12 (-38.19,-8.05)<br>2.44 (-11.28,16.17) | 15.42 (5.19,25.66)<br>7.82 (-3.05,18.69)<br>-0.65 (-10.00,8.70)  |
| 4b. The difference in the change in <b>objective redness</b> (AU) on the antecubital fossa measured by mexameter                                       | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | -20.54 (-36.28,-4.80)<br>-8.39 (-25.89,9.10)<br>10.35 (-7.84,28.54)   | -31.17 (-46.93,-15.41)<br>-20.58 (-38.09,-3.08)<br>4.82 (-13.38,23.02) | 10.63 (-1.86,23.11)<br>12.19 (-2.68,27.06)<br>5.52 (-9.84,20.88) |
| 4c. The difference in the change in <b>objective redness</b> (AU) on the cheek measured by mexameter                                                   | Baseline to day 15<br>Baseline to day 57                       | 3.31 (-11.40,18.01)<br>-3.12 (-18.61,12.36)                           | -15.00 (-29.70,-0.30)<br>-8.13 (-23.62,7.35)                           | 18.31 (2.22,34.39)<br>5.01 (-11.97,21.99)                        |
| 5a. The difference in the change in <b>TEWL</b> (g/m <sup>2</sup> /h) on the volar forearm                                                             | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | 0.39 (-0.50,1.29)<br>0.04 (-0.95,1.02)<br>1.45 (-0.68,3.59)           | -0.63 (-1.52,0.27)<br>-1.68 (-2.66,-0.70)<br>-0.02 (-2.16,2.12)        | 1.02 (0.35,1.69)<br>1.72 (0.95,2.48)<br>1.47 (-0.46,3.40)        |
| 5b. The difference in the change in <b>TEWL</b> (g/m <sup>2</sup> /h) on the antecubital fossa                                                         | Baseline to day 15<br>Baseline to day 29<br>Baseline to day 57 | -0.72 (-2.02,0.58)<br>-2.09 (-3.34,-0.84)<br>2.15 (-0.53,4.83)        | -3.19 (-4.49,-1.89)<br>-3.56 (-4.81,-2.32)<br>-0.78 (-3.46,1.90)       | 2.47 (1.25,3.70)<br>1.47 (0.33,2.62)<br>2.93 (-0.07,5.94)        |
| 5c. The difference in the change in <b>TEWL</b> (g/m <sup>2</sup> /h) on the cheek                                                                     | Baseline to day 15<br>Baseline to day 57                       | -1.05 (-2.20,0.10)<br>-0.99 (-2.24,0.27)                              | -3.82 (-4.97,-2.67)<br>-0.45 (-1.71,0.80)                              | 2.77 (1.79,3.74)<br>-0.53 (-1.64,0.57)                           |
| 6a. The difference in the change in <b>skin barrier integrity</b> measured by tape strip TEWL <sub>20</sub> (g/m <sup>2</sup> /h) on the volar forearm | Baseline to day 29                                             | -5.38 (-10.90,0.15)                                                   | -4.97 (-10.50,0.56)                                                    | -0.41 (-8.22,7.41)                                               |
| 6b. The difference in <b>skin barrier integrity</b> measured by tape strip TEWL <sub>10</sub> (g/m <sup>2</sup> /h) on the antecubital fossa           | Day 29                                                         | 29.28 (25.48,33.07)                                                   | 29.13 (23.98,34.28)                                                    | 0.15 (-4.09,4.39)                                                |

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ISRCTN52806782

| Outcome                                                                 | Day 1 | Day 15  |        |       |   |          |
|-------------------------------------------------------------------------|-------|---------|--------|-------|---|----------|
|                                                                         |       | 0       | 1      | 2     | 3 | Total    |
| 7a. The difference in the change in visual dryness on the volar forearm | CRBo  |         |        |       |   |          |
|                                                                         | 0     | 20 (51) | 1 (3)  | -     | - | 21 (54)  |
|                                                                         | 1     | 11 (28) | 4 (10) | -     | - | 15 (38)  |
|                                                                         | 2     | 2 (5)   | 1 (3)  | -     | - | 3 (8)    |
|                                                                         | 3     | -       | -      | -     | - | -        |
|                                                                         | Total | 33 (85) | 6 (15) | -     | - | 39 (100) |
|                                                                         | BMVc  |         |        |       |   |          |
|                                                                         | 0     | 23 (59) | 1 (3)  | -     | - | 24 (62)  |
|                                                                         | 1     | 6 (15)  | 4 (10) | -     | - | 10 (26)  |
|                                                                         | 2     | 3 (8)   | -      | 1 (3) | - | 4 (10)   |
|                                                                         | 3     | 1 (3)   | -      | -     | - | 1 (3)    |
|                                                                         | Total | 33 (85) | 5 (13) | 1 (3) | - | 39 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                                 | Day 1 | Day 29  |        |       |       |          |
|-------------------------------------------------------------------------|-------|---------|--------|-------|-------|----------|
|                                                                         |       | 0       | 1      | 2     | 3     | Total    |
| 7b. The difference in the change in visual dryness on the volar forearm | CRBo  |         |        |       |       |          |
|                                                                         | 0     | 18 (47) | 2 (5)  | -     | -     | 20 (53)  |
|                                                                         | 1     | 14 (37) | 1 (3)  | -     | -     | 15 (39)  |
|                                                                         | 2     | 1 (3)   | 2 (5)  | -     | -     | 3 (8)    |
|                                                                         | 3     | -       | -      | -     | -     | -        |
|                                                                         | Total | 33 (87) | 5 (13) | -     | -     | 38 (100) |
|                                                                         | BMVc  |         |        |       |       |          |
|                                                                         | 0     | 17 (45) | 6 (16) | -     | -     | 23 (61)  |
|                                                                         | 1     | 7 (18)  | 2 (5)  | 1 (3) | -     | 10 (26)  |
|                                                                         | 2     | 2 (5)   | -      | -     | 2 (5) | 4 (11)   |
|                                                                         | 3     | -       | 1 (3)  | -     | -     | 1 (3)    |
|                                                                         | Total | 26 (68) | 9 (24) | 1 (3) | 2 (5) | 38 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                                 | Day 1 | Day 57  |        |       |       |          |
|-------------------------------------------------------------------------|-------|---------|--------|-------|-------|----------|
|                                                                         |       | 0       | 1      | 2     | 3     | Total    |
| 7c. The difference in the change in visual dryness on the volar forearm | CRBo  |         |        |       |       |          |
|                                                                         | 0     | 17 (45) | 2 (5)  | -     | 1 (3) | 20 (53)  |
|                                                                         | 1     | 12 (32) | 2 (5)  | 1 (3) | -     | 15 (39)  |
|                                                                         | 2     | 1 (3)   | 1 (3)  | -     | 1 (3) | 3 (8)    |
|                                                                         | 3     | -       | -      | -     | -     | -        |
|                                                                         | Total | 30 (79) | 5 (13) | 1 (3) | 2 (5) | 38 (100) |
|                                                                         | BMVc  |         |        |       |       |          |
|                                                                         | 0     | 20 (53) | 3 (8)  | -     | -     | 23 (61)  |
|                                                                         | 1     | 7 (18)  | 1 (3)  | 1 (3) | 1 (3) | 10 (26)  |
|                                                                         | 2     | 2 (5)   | -      | 1 (3) | 1 (3) | 4 (11)   |
|                                                                         | 3     | -       | 1 (3)  | -     | -     | 1 (3)    |
|                                                                         | Total | 29 (76) | 5 (13) | 2 (5) | 2 (5) | 38 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                                     | Day 1 | Day 15  |         |        |   |          |
|-----------------------------------------------------------------------------|-------|---------|---------|--------|---|----------|
|                                                                             |       | 0       | 1       | 2      | 3 | Total    |
| 7d. The difference in the change in visual dryness on the antecubital fossa | CRBo  |         |         |        |   |          |
|                                                                             | 0     | 10 (26) | -       | -      | - | 10 (26)  |
|                                                                             | 1     | 10 (26) | 6 (15)  | 2 (5)  | - | 18 (46)  |
|                                                                             | 2     | 5 (13)  | 4 (10)  | 1 (3)  | - | 10 (26)  |
|                                                                             | 3     | -       | -       | -      | - | -        |
|                                                                             | 4     | 1 (3)   | -       | -      | - | 1 (3)    |
|                                                                             | Total | 26 (67) | 10 (26) | 3 (8)  | - | 39 (100) |
|                                                                             | BMVc  |         |         |        |   |          |
|                                                                             | 0     | 9 (23)  | 2 (5)   | -      | - | 11 (28)  |
|                                                                             | 1     | 15 (38) | 3 (8)   | 3 (8)  | - | 21 (54)  |
|                                                                             | 2     | 3 (8)   | 3 (8)   | -      | - | 6 (15)   |
|                                                                             | 3     | -       | -       | -      | - | -        |
|                                                                             | 4     | -       | -       | 1 (3)  | - | 1 (3)    |
|                                                                             | Total | 27 (69) | 8 (21)  | 4 (10) | - | 39 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                                     | Day 1 | Day 29  |         |        |       |          |
|-----------------------------------------------------------------------------|-------|---------|---------|--------|-------|----------|
|                                                                             |       | 0       | 1       | 2      | 3     | Total    |
| 7e. The difference in the change in visual dryness on the antecubital fossa | CRBo  |         |         |        |       |          |
|                                                                             | 0     | 8 (21)  | 2 (5)   | -      | -     | 10 (25)  |
|                                                                             | 1     | 10 (25) | 7 (18)  | -      | -     | 17 (45)  |
|                                                                             | 2     | 6 (16)  | 3 (8)   | -      | 1 (3) | 10 (25)  |
|                                                                             | 3     | 1 (3)   | -       | -      | -     | 1 (3)    |
|                                                                             | Total | 24 (63) | 12 (32) | 1 (3)  | 1 (3) | 38 (100) |
|                                                                             | BMVc  |         |         |        |       |          |
|                                                                             | 0     | 5 (13)  | 3 (8)   | 2 (5)  | -     | 10 (25)  |
|                                                                             | 1     | 8 (21)  | 9 (24)  | 3 (8)  | 1 (3) | 21 (55)  |
|                                                                             | 2     | 3 (8)   | 2 (5)   | 1 (3)  | -     | 6 (16)   |
|                                                                             | 3     | -       | -       | -      | 1 (3) | 1 (3)    |
|                                                                             | 4     | 1 (3)   | -       | -      | 1 (3) | 1 (3)    |
|                                                                             | Total | 17 (45) | 14 (37) | 6 (16) | 3 (8) | 39 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                                     | Day 1 | Day 57  |         |        |       |          |
|-----------------------------------------------------------------------------|-------|---------|---------|--------|-------|----------|
|                                                                             |       | 0       | 1       | 2      | 3     | Total    |
| 7f. The difference in the change in visual dryness on the antecubital fossa | CRBo  |         |         |        |       |          |
|                                                                             | 0     | 6 (16)  | 4 (11)  | -      | -     | 10 (26)  |
|                                                                             | 1     | 8 (21)  | 7 (18)  | 2 (5)  | -     | 17 (45)  |
|                                                                             | 2     | 2 (5)   | 3 (8)   | 5 (13) | -     | 10 (26)  |
|                                                                             | 3     | -       | -       | -      | -     | -        |
|                                                                             | 4     | -       | -       | -      | 1 (3) | 1 (3)    |
|                                                                             | Total | 16 (42) | 14 (37) | 7 (18) | 1 (3) | 38 (100) |
|                                                                             | BMVc  |         |         |        |       |          |
|                                                                             | 0     | 5 (13)  | 4 (11)  | 1 (3)  | -     | 10 (26)  |
|                                                                             | 1     | 10 (26) | 10 (26) | 1 (3)  | -     | 21 (55)  |
|                                                                             | 2     | -       | 5 (13)  | 1 (3)  | -     | 6 (16)   |
|                                                                             | 3     | -       | -       | -      | -     | -        |
|                                                                             | 4     | -       | -       | 1 (3)  | -     | 1 (3)    |
|                                                                             | Total | 15 (39) | 19 (50) | 4 (11) | -     | 38 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                         | Day 1 | Day 15  |        |        |   |          |
|-----------------------------------------------------------------|-------|---------|--------|--------|---|----------|
|                                                                 |       | 0       | 1      | 2      | 3 | Total    |
| 7g. The difference in the change in visual dryness on the cheek | CRBo  |         |        |        |   |          |
|                                                                 | 0     | 20 (51) | 1 (3)  | -      | - | 21 (54)  |
|                                                                 | 1     | 7 (18)  | 4 (10) | 2 (5)  | - | 13 (33)  |
|                                                                 | 2     | 2 (5)   | 1 (3)  | 1 (3)  | - | 4 (10)   |
|                                                                 | 3     | -       | -      | 1 (3)  | - | 1 (3)    |
|                                                                 | Total | 29 (74) | 6 (15) | 4 (10) | - | 39 (100) |
|                                                                 | BMVc  |         |        |        |   |          |
|                                                                 | 0     | 22 (56) | -      | -      | - | 22 (56)  |
|                                                                 | 1     | 5 (13)  | 5 (13) | 1 (3)  | - | 11 (28)  |
|                                                                 | 2     | 3 (8)   | 1 (3)  | 1 (3)  | - | 5 (13)   |
|                                                                 | 3     | -       | -      | 1 (3)  | - | 1 (3)    |
|                                                                 | Total | 30 (77) | 6 (15) | 3 (8)  | - | 39 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

| Outcome                                                         | Day 1 | Day 57  |         |       |   |          |
|-----------------------------------------------------------------|-------|---------|---------|-------|---|----------|
|                                                                 |       | 0       | 1       | 2     | 3 | Total    |
| 7h. The difference in the change in visual dryness on the cheek | CRBo  |         |         |       |   |          |
|                                                                 | 0     | 13 (34) | 7 (18)  | -     | - | 20 (53)  |
|                                                                 | 1     | 4 (11)  | 8 (21)  | 1 (3) | - | 13 (34)  |
|                                                                 | 2     | -       | 3 (8)   | 1 (3) | - | 4 (11)   |
|                                                                 | 3     | -       | 1 (3)   | -     | - | 1 (3)    |
|                                                                 | Total | 17 (45) | 19 (50) | 2 (5) | - | 38 (100) |
|                                                                 | BMVc  |         |         |       |   |          |
|                                                                 | 0     | 14 (37) | 7 (18)  | -     | - | 21 (55)  |
|                                                                 | 1     | 4 (11)  | 7 (18)  | -     | - | 11 (29)  |
|                                                                 | 2     | -       | 3 (8)   | 2 (5) | - | 5 (13)   |
|                                                                 | 3     | -       | 1 (3)   | -     | - | 1 (3)    |
|                                                                 | Total | 18 (47) | 18 (47) | 2 (5) | - | 38 (100) |

Shift table of investigator visual dryness scores, *n* (%): 0 – Absent; 1 – Faint roughness, white appearance; 2 – Small scales, slight roughness, 3 – Small and large uniform scales, definite roughness; 4 – Large scales, advanced roughness, redness and superficial cracks.

## Adverse events

| System Organ Class                                   | Preferred Term                                                                                                                                                                  | Total participants N=40                                                        |
|------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Any adverse event                                    |                                                                                                                                                                                 | 35 (88)                                                                        |
| Eye disorders                                        | Eye pruritus                                                                                                                                                                    | 1 (3)                                                                          |
| Gastrointestinal disorders                           | Abdominal pain upper<br>Nausea                                                                                                                                                  | 1 (3)<br>1 (3)                                                                 |
| General disorders and administration site conditions | Application site hypersensitivity<br>Application site pain<br>Pain*                                                                                                             | 1 (3)<br>5 (13)<br>21 (53)                                                     |
| Immune system disorders                              | Hypersensitivity<br>Seasonal allergy                                                                                                                                            | 1 (3)<br>2 (5)                                                                 |
| Infections and infestations                          | Candida infection<br>Cystitis<br>Gingivitis<br>Infection<br>Nasopharyngitis<br>Pneumonia<br>Respiratory tract infection<br>Upper respiratory tract infection<br>Viral infection | 1 (3)<br>1 (3)<br>1 (3)<br>1 (3)<br>2 (5)<br>1 (3)<br>2 (5)<br>5 (13)<br>1 (3) |
| Injury, poisoning and procedural complications       | Contusion<br>Eye injury<br>Scratch<br>Skin abrasion<br>Sunburn<br>Wound                                                                                                         | 2 (5)<br>1 (3)<br>1 (3)<br>4 (10)<br>1 (3)<br>2 (5)                            |
| Investigations                                       | Biopsy                                                                                                                                                                          | 1 (3)                                                                          |
| Musculoskeletal and connective tissue disorders      | Arthralgia<br>Fibromyalgia                                                                                                                                                      | 1 (3)<br>1 (3)                                                                 |
| Nervous system disorders                             | Headache                                                                                                                                                                        | 10 (25)                                                                        |
| Psychiatric disorders                                | Depression                                                                                                                                                                      | 1 (3)                                                                          |
| Reproductive system and breast disorders             | Dysmenorrhoea                                                                                                                                                                   | 3 (8)                                                                          |
| Respiratory, thoracic and mediastinal disorders      | Oropharyngeal pain                                                                                                                                                              | 1 (3)                                                                          |
| Skin and subcutaneous tissue disorders               | Dry skin<br>Eczema<br>Pruritus<br>Scab<br>Skin exfoliation                                                                                                                      | 3 (8)<br>6 (15)<br>1 (3)<br>1 (3)<br>1 (3)                                     |

\*Includes burning/stinging/tingling sensations experienced upon application. Adverse events were recorded directly as reported by the participant. % in brackets.