Subgroup analysis of crisaborole for mild-to-moderate atopic dermatitis in children aged 2 to <18 years

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aAt the time of the analysis.

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Table S1 Baseline characteristics for the pediatric population (aged 2 to <18 years) for individual studies

|                         | AD-301 Vehicle N = 218 | Crisaborole N = 438 | AD-302 Vehicle N = 221 | Crisaborole N = 436 |
|-------------------------|-------------------------|----------------------|-------------------------|----------------------|
| Age groups, n (%)       |                         |                      |                         |                      |
| 2 to <7 years           | 78 (35.8)               | 162 (37.0)           | 93 (42.1)               | 173 (39.7)           |
| 7 to <12 years          | 73 (33.5)               | 155 (35.4)           | 71 (32.1)               | 137 (31.4)           |
| 12 to <18 years         | 67 (30.7)               | 121 (27.6)           | 57 (25.8)               | 126 (28.9)           |
| Sex, n (%)              |                         |                      |                         |                      |
| Male                    | 101 (46.3)              | 201 (45.9)           | 106 (48.0)              | 207 (47.5)           |
| Female                  | 117 (53.7)              | 237 (54.1)           | 115 (52.0)              | 229 (52.5)           |
| ISGA, n (%)             |                         |                      |                         |                      |
| Mild (2)                | 78 (35.8)               | 168 (38.4)           | 89 (40.3)               | 165 (37.8)           |
| Moderate (3)            | 140 (64.2)              | 270 (61.6)           | 132 (59.7)              | 271 (62.2)           |
| SPS\(^a\) N = 163       | 1.7 (0.82)              | 1.8 (0.79)           | 1.8 (0.70)              | 1.8 (0.80)           |
| %BSA severity, n (%)    |                         |                      |                         |                      |
| Mild (5 to <16)         | 134 (61.5)              | 274 (62.5)           | 129 (58.4)              | 277 (63.5)           |
| Moderate (≥16 to <40)   | 56 (25.7)               | 108 (24.7)           | 72 (32.6)               | 105 (24.1)           |
| Severe (≥40)            | 28 (12.8)               | 56 (12.8)            | 20 (9.0)                | 54 (12.4)            |
| Use of prior AD treatment,\(^b\) n (%) | 91 (41.7)              | 171 (39.0)           | 123 (55.7)              | 200 (45.9)           |
| No                      | 127 (58.3)              | 267 (61.0)           | 98 (44.3)               | 236 (54.1)           |

%BSA percentage of treatable body surface area, AD atopic dermatitis, ISGA Investigator’s Static Global Assessment, SD standard deviation, SPS Severity of Pruritus Scale

\(^a\)Baseline pruritus was the average of ≥2 assessments on day 1

\(^b\)Defined as any prior use of systemic corticosteroids, topical corticosteroids, or topical calcineurin inhibitors for the treatment of AD within 90 days of study screening
Table S2  Safety summary for the adult population (aged ≥18 years)

|                                      | AD-301 Vehicle N = 37 | AD-302 Vehicle N = 29 | AD-301 + AD-302 pooled Vehicle N = 66 | AD-301 Crisaborole N = 65 | AD-302 Crisaborole N = 76 | AD-301 + AD-302 pooled Crisaborole N = 141 |
|--------------------------------------|------------------------|------------------------|----------------------------------------|---------------------------|---------------------------|---------------------------------------------|
| **TEAEs (all cause), n (%)**         | 6 (16.2)               | 15 (23.1)              | 8 (27.6)                               | 23 (30.3)                 | 14 (21.2)                 | 38 (27.0)                                   |
| **TEAEs leading to discontinuation (all cause), n (%)** | 0                      | 0                      | 0                                      | 0                         | 0                         | 0                                           |
| **Treatment-related AEs, n (%)**     | 3 (8.1)                | 6 (9.2)                | 3 (10.3)                               | 5 (6.6)                   | 6 (9.1)                   | 11 (7.8)                                    |
| **Incidence of treatment-related application site pain, n (%)** | 1 (2.7)                | 4 (6.2)                | 1 (3.4)                                | 3 (3.9)                   | 2 (3.0)                   | 7 (5.0)                                     |
| **Duration of application site pain, days** | NA                    | 5                      | 1                                      | 3                         | 1                         | 8                                           |
|                                      |                        |                        | Mean (SD)                              |                           |                           | 17.0 (9.21)                                |
|                                      |                        |                        | 17.0 (NA)                              | 1.3 (0.58)                | 17.0 (NA)                 | 11.4 (10.85)                               |
| **Median (range)**                   |                        | 22.0 (1–22)            | 17.0 (NA)                              | 1.0 (1–2)                 | 17.0 (NA)                 | 11.0 (1–22)                                |

*AE adverse event, NA not applicable; SD standard deviation; TEAE treatment-emergent adverse event*
Table S3 Incidence of treatment-related application site pain in the pediatric population (aged 2 to <18 years) for individual studies

|                          | AD-301 Vehicle N = 215 | Crisaborole N = 437 | AD-302 Vehicle N = 218 | Crisaborole N = 434 |
|--------------------------|------------------------|---------------------|------------------------|---------------------|
| All pediatric patients, n (%) | 2 (0.9) | 27 (6.2) | 2 (0.9) | 11 (2.5) |
| Age group, n/N (%)     |                       |                     |                        |                     |
| 2 to <7 years           | 1/77 (1.3) | 9/161 (5.6) | 1/91 (1.1) | 3/172 (1.7) |
| 7 to <12 years          | 1/72 (1.4) | 12/155 (7.7) | 0/71 (0) | 4/137 (2.9) |
| 12 to <18 years         | 0/66 (0) | 6/121 (5.0) | 1/56 (1.8) | 4/125 (3.2) |
| Sex, n/N (%)            |                       |                     |                        |                     |
| Male                    | 1/99 (1.0) | 15/200 (7.5) | 1/104 (1.0) | 3/206 (1.5) |
| Female                  | 1/116 (0.9) | 12/237 (5.1) | 1/114 (0.9) | 8/228 (3.5) |
| Baseline ISGA, n/N (%)  |                       |                     |                        |                     |
| Mild (2)                | 0/77 (0) | 6/168 (3.6) | 1/89 (1.1) | 2/164 (1.2) |
| Moderate (3)            | 2/138 (1.4) | 21/269 (7.8) | 1/129 (0.8) | 9/270 (3.3) |
| Baseline %BSA severity, n/N (%) |          |                     |                        |                     |
| Mild (5 to <16)         | 1/132 (0.8) | 14/273 (5.1) | 1/128 (0.8) | 5/276 (1.8) |
| Moderate (≥16 to <40)   | 1/55 (1.8) | 5/108 (4.6) | 0/72 (0) | 3/105 (2.9) |
| Severe (≥40)            | 0/28 (0) | 8/56 (14.3) | 1/18 (5.6) | 3/53 (5.7) |
| Use of prior AD treatment, n/N (%) |  |                     |                        |                     |
| Yes                     | 1/91 (1.1) | 18/170 (10.6) | 1/121 (0.8) | 7/199 (3.5) |
| No                      | 1/124 (0.8) | 9/267 (3.4) | 1/97 (1.0) | 4/235 (1.7) |

%BSA percentage of treatable body surface area, AD atopic dermatitis, ISGA Investigator’s Static Global Assessment

*Defined as any prior use of systemic corticosteroids, topical corticosteroids, or topical calcineurin inhibitors for the treatment of AD within 90 days of study screening
### Table S4 Duration of treatment-related application site pain by age group (AD-301 + AD-302 pooled)

| Age Group                | Vehicle | Crisaborole |
|--------------------------|---------|-------------|
| **n**                    | 5       | 44          |
| **Mean (SD)**            | 1.8 (0.45) | 4.3 (8.08) |
| **Median (range)**       | 2.0 (1–2) | 1.0 (1–30) |
| **Aged 2 to <7 years**   |         |             |
| **n**                    | 2       | 12          |
| **Mean (SD)**            | 2.0 (0) | 3.3 (5.67)  |
| **Median (range)**       | 2.0 (2–2) | 1.0 (1–21)  |
| **Aged 7 to <12 years**  |         |             |
| **n**                    | 1       | 19          |
| **Mean (SD)**            | 2.0 (NA) | 4.2 (7.66)  |
| **Median (range)**       | 2.0 (2–2) | 1.0 (1–28)  |
| **Aged 12 to <18 years** |         |             |
| **n**                    | 2       | 13          |
| **Mean (SD)**            | 1.5 (0.71) | 5.5 (10.67) |
| **Median (range)**       | 1.5 (1–2) | 1.0 (1–30)  |

*NA* not applicable, *SD* standard deviation
Table S5 Duration of treatment-related application site pain by age group for individual studies

| Age Group               | n  | AD-301 Vehicle | AD-301 Crisaborole | AD-302 Vehicle | AD-302 Crisaborole |
|-------------------------|----|----------------|--------------------|----------------|--------------------|
| Aged 2 to <18 years     |    |                |                    |                |                    |
| n                       | 2  | 32             | 3                  | 12             |                    |
| Mean (SD)               | 2.0 (0.00) | 5.6 (9.20) | 1.7 (0.58) | 1.0 (0.00) |
| Median (range)          | 2.0 (2–2) | 1.0 (1–30) | 2.0 (1–2) | 1.0 (1–1) |
| Age 2 to <7 years       |    |                |                    |                |                    |
| n                       | 1  | 10             | 2                  | 2              |                    |
| Mean (SD)               | 2.0 (NA) | 3.7 (6.17) | 1.5 (0.71) | 1.0 (0.00) |
| Median (range)          | 2.0 (NA) | 1.5 (1–21) | 1.5 (1–2) | 1.0 (1–1) |
| Age 7 to <12 years      |    |                |                    |                |                    |
| n                       | 1  | 14             | NA                | 5              |                    |
| Mean (SD)               | 2.0 (NA) | 5.4 (8.71) | NA               | 1.0 (0.00) |
| Median (range)          | 2.0 (NA) | 1.0 (1–28) | NA               | 1.0 (1–1) |
| Age 12 to <18 years     |    |                |                    |                |                    |
| n                       | NA | 8              | 1                  | 5              |                    |
| Mean (SD)               | NA | 8.3 (13.12) | 2.0 (NA) | 1.0 (0.00) |
| Median (range)          | NA | 1.0 (1–30) | 2.0 (NA) | 1.0 (1–1) |

NA not applicable, SD standard deviation
**Fig S1** Proportions of patients achieving ISGA success\(^a\) at day 29 (week 4) in the pediatric population (aged 2 to <18 years) by individual study

| Subgroup                  | Crisaborole Patients/ Rate | Vehicle Patients/ Rate | AD-301 Difference in ISGA Success* Rate (95% CI) | AD-302 Difference in ISGA Success* Rate (95% CI) | Crisaborole Patients/ Rate | Vehicle Patients/ Rate |
|---------------------------|-----------------------------|------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------|------------------------|
| All pediatric patients    | 438 33.0%                   | 219 25.9%              |                                               |                                               | 436 32.0%                   | 221 16.8%              |
| Age group                 |                             |                        |                                               |                                               |                             |                        |
| 2 to <7 years             | 162 33.6%                   | 78 32.1%               |                                               |                                               | 173 27.4%                   | 93 12.4%               |
| 7 to <12 years            | 155 31.4%                   | 73 25.4%               |                                               |                                               | 137 42.9%                   | 71 20.1%               |
| 12 to <18 years           | 121 34.2%                   | 67 19.2%               |                                               |                                               | 126 26.3%                   | 57 19.7%               |
| Sex                       |                             |                        |                                               |                                               |                             |                        |
| Male                      | 201 32.6%                   | 101 27.8%              |                                               |                                               | 207 34.0%                   | 106 20.5%              |
| Female                    | 237 33.3%                   | 117 24.3%              |                                               |                                               | 229 30.2%                   | 115 13.4%              |
| Baseline ISGA             |                             |                        |                                               |                                               |                             |                        |
| Mild                      | 168 23.7%                   | 78 27.8%               |                                               |                                               | 165 26.5%                   | 89 15.7%               |
| Moderate                  | 270 38.8%                   | 140 24.8%              |                                               |                                               | 271 35.3%                   | 132 17.5%              |
| Baseline %BSA severity    |                             |                        |                                               |                                               |                             |                        |
| Mild                      | 274 32.9%                   | 134 27.7%              |                                               |                                               | 277 32.0%                   | 129 19.4%              |
| Moderate                  | 108 36.6%                   | 56 21.7%               |                                               |                                               | 105 37.6%                   | 72 14.9%               |
| Severe                    | 56 22.6%                    | 28 25.5%               |                                               |                                               | 54 21.0%                    | 20 6.8%                |
| Use of prior AD treatment |                             |                        |                                               |                                               |                             |                        |
| Yes                       | 171 32.8%                   | 91 20.4%               |                                               |                                               | 200 26.0%                   | 123 11.5%              |
| No                        | 267 33.1%                   | 127 29.8%              |                                               |                                               | 236 37.1%                   | 98 22.9%               |

\(^a\)Defined as an ISGA of clear (0) or almost clear (1) with ≥2-grade improvement from baseline

\(^b\)Defined as any prior use of systemic corticosteroids, topical corticosteroids, or topical calcineurin inhibitors for the treatment of AD within 90 days of study screening
Fig S2 Efficacy outcomes at day 29 (week 4) in the adult population (aged ≥18 years) in (A) AD-301 + AD-302 pooled and (B) by individual study

**a** Defined as a score of clear (0) or almost clear (1) with ≥2-grade improvement from baseline

**b** SPS success is defined as a weekly average SPS score ≤1 point with ≥1-point improvement from baseline
Fig S3 Proportions of patients achieving ISGA clear or almost clear at day 29 (week 4) in the pediatric population (aged 2 to <18 years) by individual study

| Subgroup                        | Crisaborole Patients/ Rate | Vehicle Patients/ Rate | AD-301 Difference in ISGA Clear/Almost Clear Rate (95% CI) | AD-302 Difference in ISGA Clear/Almost Clear Rate (95% CI) | Crisaborole Patients/ Rate | Vehicle Patients/ Rate |
|---------------------------------|-----------------------------|------------------------|------------------------------------------------------------|------------------------------------------------------------|-----------------------------|------------------------|
| All pediatric patients         | 438                         | 218                    | 218 40.9%                                                  | 436 49.0%                                                  | 221                         | 27.7%                  |
| Age group                      |                             |                        |                                                            |                                                            |                             |                        |
| 2 to <7 years                  | 162                         | 78                     | 78 38.5%                                                   | 173 46.5%                                                  | 93                          | 25.3%                  |
| 7 to <12 years                 | 155                         | 73                     | 73 42.4%                                                   | 137 58.2%                                                  | 71                          | 32.7%                  |
| 12 to <18 years                | 121                         | 67                     | 67 41.9%                                                   | 126 42.5%                                                  | 57                          | 25.5%                  |
| Sex                             |                             |                        |                                                            |                                                            |                             |                        |
| Male                           | 201                         | 101                    | 101 40.0%                                                  | 207 49.8%                                                  | 106                         | 32.2%                  |
| Female                         | 237                         | 117                    | 117 41.6%                                                  | 229 48.3%                                                  | 115                         | 23.6%                  |
| Baseline ISGA                  |                             |                        |                                                            |                                                            |                             |                        |
| Mild                           | 168                         | 78                     | 78 69.7%                                                   | 165 71.6%                                                  | 89                          | 43.0%                  |
| Moderate                       | 270                         | 140                    | 140 24.8%                                                  | 271 35.3%                                                  | 132                         | 17.5%                  |
| Baseline %BSA severity         |                             |                        |                                                            |                                                            |                             |                        |
| Mild                           | 274                         | 134                    | 134 48.6%                                                  | 277 55.3%                                                  | 129                         | 34.0%                  |
| Moderate                       | 108                         | 56                     | 56 27.7%                                                   | 105 43.6%                                                  | 72                          | 21.0%                  |
| Severe                         | 56                          | 28                     | 28 29.0%                                                   | 54                          | 20                          | 11.8%                  |
| Use of prior AD treatment*     |                             |                        |                                                            |                                                            |                             |                        |
| Yes                            | 171                         | 91                     | 91 30.7%                                                   | 200 41.3%                                                  | 123                         | 24.1%                  |
| No                             | 267                         | 127                    | 127 48.2%                                                  | 236                         | 98                          | 32.3%                  |

*Defined as any prior use of systemic corticosteroids, topical corticosteroids, or topical calcineurin inhibitors for the treatment of AD within 90 days of study screening
**Fig S4** Proportions of patients achieving SPS success\(^a\) at week 4 in the pediatric population (age 2 to <18 years) by individual study

| Subgroup                        | Crisaborole Patients/Rate | Vehicle Patients/Rate | AD-301 Difference in SPS Success\(^a\) Rate (95% CI) | AD-302 Difference in SPS Success\(^a\) Rate (95% CI) | Crisaborole Patients/Rate | Vehicle Patients/Rate |
|---------------------------------|---------------------------|-----------------------|---------------------------------------------------|---------------------------------------------------|---------------------------|-----------------------|
| All pediatric patients          |                           |                       |                                                   |                                                   |                           |                       |
| 2 to <18 years                  | 324                       | 145                   | 20.7%                                            |                                                  | 306                       | 145                   |
| Age group                       |                           |                       |                                                   |                                                   |                           |                       |
| 2 to <7 years                   | 123                       | 51                    | 21.6%                                            |                                                  | 116                       | 52                    |
| 7 to <12 years                  | 112                       | 50                    | 20.0%                                            |                                                  | 97                        | 53                    |
| 12 to <18 years                 | 89                        | 44                    | 20.5%                                            |                                                  | 93                        | 40                    |
| Sex                             |                           |                       |                                                   |                                                   |                           |                       |
| Male                            | 148                       | 66                    | 18.2%                                            |                                                  | 149                       | 68                    |
| Female                          | 176                       | 79                    | 22.8%                                            |                                                  | 157                       | 77                    |
| Baseline ISGA                   |                           |                       |                                                   |                                                   |                           |                       |
| Mild                            | 125                       | 55                    | 27.3%                                            |                                                  | 115                       | 55                    |
| Moderate                        | 199                       | 90                    | 16.7%                                            |                                                  | 191                       | 90                    |
| Baseline %BSA severity          |                           |                       |                                                   |                                                   |                           |                       |
| Mild                            | 199                       | 91                    | 23.1%                                            |                                                  | 200                       | 87                    |
| Moderate                        | 88                        | 36                    | 16.7%                                            |                                                  | 71                        | 50                    |
| Severe                          | 37                        | 18                    | 16.7%                                            |                                                  | 35                        | 8                     |
| Use of prior AD treatment\(^b\) |                           |                       |                                                   |                                                   |                           |                       |
| Yes                             | 127                       | 59                    | 18.6%                                            |                                                  | 139                       | 82                    |
| No                              | 197                       | 86                    | 22.1%                                            |                                                  | 167                       | 63                    |

\(^a\)Defined as weekly average SPS score ≤1 with ≥1-point improvement from baseline

\(^b\)Defined as any prior use of systemic corticosteroids, topical corticosteroids, or topical calcineurin inhibitors for the treatment of AD within 90 days of study screening