Supplemental Material 1. Treatment sequences for the 3-way crossover studies of ubrogepant drug-drug interactions with acetaminophen or naproxen.

| Sequence | Period 1 | Period 2 | Period 3 |
|----------|----------|----------|----------|
| 1        | A        | B        | C        |
| 2        | A        | C        | B        |
| 3        | B        | A        | C        |
| 4        | B        | C        | A        |
| 5        | C        | A        | B        |
| 6        | C        | B        | A        |

In Study A, Treatment A = single oral 1000 mg acetaminophen dose (2 × 500 mg tablets) alone, Treatment B = single oral 100 mg ubrogepant therapeutic dose (2 × 50 mg tablets) alone, and Treatment C = single oral 100 mg ubrogepant dose + 1000 mg acetaminophen dose. In Study B, Treatment A = single oral 100 mg ubrogepant dose (2 × 50 mg tablets) alone, Treatment B = single oral 500 mg naproxen dose alone, and Treatment C = single oral 100 mg ubrogepant dose + 500 mg naproxen dose.
Supplemental Material 2. Patient Disposition, Study A.
Supplemental Material 3. Patient Disposition, Study B.

Randomized (n=30)

Allocated to ABC (n=5)
- Received ABC (n=5)
- Did not receive ABC (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention (n=0)
  - Analyzed (n=5)
  - Excluded from analysis (n=0)

Allocated to ACB (n=5)
- Received ACB (n=5)
- Did not receive ACB (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention (n=0)
  - Analyzed (n=5)
  - Excluded from analysis (n=0)

Allocated to BAC (n=5)
- Received BAC (n=5)
- Did not receive BAC (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention, withdrew consent (n=1)
  - Analyzed (n=4)
  - Excluded from analysis (n=1)

Allocated to BCA (n=5)
- Received BCA (n=5)
- Did not receive BCA (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention (n=0)
  - Analyzed (n=5)
  - Excluded from analysis (n=0)

Allocated to CAB (n=5)
- Received CAB (n=5)
- Did not receive CAB (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention (n=0)
  - Analyzed (n=5)
  - Excluded from analysis (n=0)

Allocated to CBA (n=5)
- Received CBA (n=5)
- Did not receive CBA (n=0)
  - Lost to follow-up (n=0)
  - Discontinued intervention (n=0)
  - Analyzed (n=5)
  - Excluded from analysis (n=0)
**Supplemental Material 4.** Specific adverse events from ACHIEVE trials for ubrogepant alone or in combination with acetaminophen or a non-steroidal anti-inflammatory drug as rescue medication within 30 days.

| Specific adverse events, n (%) | Ubrogepant alone | Ubrogepant + NSAID\(^b\) rescue | Ubrogepant + acetaminophen rescue |
|-------------------------------|-------------------|---------------------------------|----------------------------------|
| Goiter                        | 0                 | 0                               | 1 (7.1)                          |
| Nausea                        | 7 (2.2)           | 17 (2.5)                        | 18 (5.1)                         |
| Diarrhea                      | 0                 | 0                               | 0                                |
| Abdominal pain lower          | 0                 | 0                               | 0                                |
| Constipation                  | 0                 | 0                               | 0                                |
| Dyspepsia                     | 0                 | 0                               | 0                                |
| Vomiting                      | 0                 | 0                               | 0                                |
| Dry mouth                     | 1 (0.3)           | 4 (0.6)                         | 9 (2.5)                          |
| Chills                        | 0                 | 0                               | 0                                |
| Seasonal allergy              | 0                 | 0                               | 0                                |
| Nasopharyngitis               | 4 (1.3)           | 12 (1.8)                        | 7 (2.0)                          |
| Upper                         | 0                 | 0                               | 0                                |
| Condition                        | Row Count | Column Count | Value Count | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  | 1 (7.1) | 0  |
|---------------------------------|-----------|--------------|-------------|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|---------|----|
| Respiratory tract infection     |           |              |             |         |    |         |    |         |    |         |    |         |    |         |    |         |    |         |    |         |    |
| Urinary tract infection         | 0         | 0            | 0           | 1 (2.0) | 0  | 3 (9.1) | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Vulvovaginal candidiasis        | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Helicobacter infection          | 0         | 0            | 0           | 0       | 0  | 1 (3.0) | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Tooth infection                 | 0         | 0            | 0           | 1 (2.0) | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Blood pressure diastolic increased | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Back pain                       | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Headache                        | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |         |    |
| Hypoesthesia                    | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Somnolence                      | 4 (1.3)   | 6 (0.9)      | 12 (3.4)    | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Dizziness                       | 7 (2.2)   | 15 (2.2)     | 8 (2.3)     | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Panic attack                    | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Ovarian cyst                    | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Rhinorrhea                      | 0         | 0            | 0           | 0       | 0  | 0       | 0  | 0       | 0  | 1 (7.1) | 0  |         |    |         |    |         |    |         |    |         |    |         |    |
| Concussion                      | 0         | 0            | 0           | 0       | 0  | 1 (3.0) | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Fall                            | 0         | 0            | 0           | 0       | 0  | 1 (3.0) | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  | 0       | 0  |
| Arthropod bite | 0 | 0 | 0 | 1 (2.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

NSAID: non-steroidal anti-inflammatory drug; UBRO: ubrogepant.

aPooled data across ACHIEVE I and ACHIEVE II trials.

bMedications included aspirin, diclofenac, ibuprofen, ketoprofen, and naproxen.