**Supplemental Materials**

**Application of the PET ligand [11C]ORM-13070** **to examine receptor occupancy by the α2C-adrenoceptor antagonist ORM-12741: translational validation of target engagement in rat and human brain**

Mohammed Shahid1, Juha O. Rinne2,3, Mika Scheinin4,5,6, Jere Virta2,3, Päivi Marjamäki2,7, Olof Solin2,8,9, Eveliina Arponen2, Jukka Sallinen1, Katja Kuokkanen1, Juha Rouru1

Affiliations:

1Orion Corporation, Orion Pharma, Research and Development, Espoo, Finland

2Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

3Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland

4CRST, Turku, Finland

5Institute of Biomedicine, University of Turku, Finland

6Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland

7MediCity Research Laboratory, University of Turku, Turku, Finland

8Department of Chemistry, University of Turku, Turku, Finland

9Accelerator Laboratory, Åbo Akademi University, Turku, Finland

**S1. Summary of pharmacokinetic variables after single oral doses of ORM-12741 in healthy males (n=18), for Cmax and AUCt: geometric mean (CV%), for tmax and t1/2: mean (SD)**

| ORM-12741 dose (mg) | Number of subjects (N) | Cmax(ng/mL) | tmax(h) | AUCt(h×ng/mL) | t½(h) |
| --- | --- | --- | --- | --- | --- |
| 0.3 | 2 | 1.21 (2) | 0.67 (0) | 4.50 (-)2 | 4.0 (0) |
| 1.0 | 2 | 2.69 (14) | 0.85 (0.3)  | 8.45 (1) | 5.6 (0.1)  |
| 10 | 5 | 62.6 (77) | 0.81 (0.2) | 129 (92) | 7.2 (3.3) |
| 30 | 5 | 121 (99) | 0.68 (0.02)  | 316 (51) | 6.3 (1.3)  |
| 60 | 4 | 174 (144) | 0.67 (0) | 732 (78) | 16.1 (9.5)  |
| 2N = 1 |  |  |  |  |  |

**S2. Summary of the** **α2C-AR occupancy results by time point in the caudate nucleus and putamen**

|  |  |
| --- | --- |
|  **Dose** | **0.3 mg**  |
| Time | 1 h (n = 1) | 3.5 h (n = 1) | 6 h (n = 1) | 12 h (n = 1) |
| Region | Caudate nucleus | -0.5% | -1.2% | 5.4% | -2.4% |
|  | Putamen | 1.5% | -0.3% | 4.1% | 0.2% |
|  |  |  |  |  |  |
| **Dose** | **1 mg** |
| Time | 1 h (n = 1) | 3.5 h (n = 1) | 6 h (n = 1) | 12 h (n = 1) |
| Region | Caudate nucleus | 9.6% | 8.9% | 11.2% | 9.9% |
|  | Putamen | 5.2% | 5.7% | 10.8% | 8.8% |
|  |  |  |  |  |  |
| **Dose** | **10 mg** |
| Time | 1 h (n = 3)1 | 3.5 h (n = 3) 1 | 6 h (n = 2) 1 | 12 h (n = 2) 1 |
| Region | Caudate nucleus | 32.2% | 28.1% | 11.8% | 9.9% |
|  | Putamen | 26.9% | 17.7% | 5.6% | 0.9% |
|  |  |  |  |  |  |
| **Dose** | **30 mg** |
| Time | 1 h (n = 3) 1 | 3.5 h (n = 3) 1 | 6 h (n = 2) 1 | 12 h (n = 2) 1 |
| Region | Caudate nucleus | 64.6% | 17.3% | 17.4% | 0.7% |
|  | Putamen | 48.6% | 13.7% | 15.2% | 7.6% |
|  |  |  |  |  |  |
| **Dose** | **60 mg** |
| Time | 1h (n = 4) 1 | 3.5 h (n = 4) 1 | 6.5 h (n = 4) 1 |
| Region | Caudate nucleus | 64.8% | 35.8% | 18.7% |
|  | Putamen | 49.1% | 24.8% | 13.0% |
|  |  |  |  |  |

1 Where there was more than 1 subject per ORM-12741 dose level and time point, mean values are shown

**S3. Individual α2C-AR occupancy results by time point in the caudate nucleus and putamen**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Occupancy in the caudate nucleus (%) |  | Occupancy in the putamen (%) |  | Mean ORM-12741 concentration during PET measurement (ng/ml) |
| Subject |  | 1 h | 3.5 h | 6-6.5 h | 12 h |  | 1 h | 3.5 h | 6-6.5 h | 12 h |  | 1 h | 3.5 h | 6-6.5 h | 12 h |
| 0.3 mg dose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 101 |  | -0.5 | -1.2 |  |  |  | 1.5 | -0.3 |  |  |  | 0.7 | 0.3 |  |  |
| 102 |  |  |  | 5.0 | -2.0 |  |  |  | 4.0 | 0.2 |  |  |  | 0.2 | 0.2 |
| 1 mg dose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 201 |  | 10 | 9.0 |  |  |  | 5.0 | 6.0 |  |  |  | 2.4 | 0.4 |  |  |
| 203 |  |  |  | 11 | 10 |  |  |  | 11 | 9.0 |  |  |  | 0.2 | 0.4 |
| 10 mg dose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 301 |  | 21 | 46 |  |  |  | 17 | 20 |  |  |  | 56 | 19 |  |  |
| 302 |  |  |  | 0.3 | 0.3 |  |  |  | 0.4 | -1.6 |  |  |  | 1.3 | 1.2 |
| 303 |  |  |  | 23 | 20 |  |  |  | 11 | 3.0 |  |  |  | 1.4 | 2.1 |
| 304 |  | 42 | 16 |  |  |  | 35 | 15 |  |  |  | 115 | 15 |  |  |
| 305 |  | 33 | 22 |  |  |  | 29 | 18 |  |  |  | 21 | 4.4 |  |  |
| 30 mg dose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 401 |  |  |  | 7.0 | -21 |  |  |  | 9.0 | 0.3 |  |  |  | 4.1 | 5.6 |
| 402 |  | 65 | 22 |  |  |  | 55 | 18 |  |  |  | 44 | 13 |  |  |
| 403 |  | 70 | 18 |  |  |  | 48 | 14 |  |  |  | 123 | 28 |  |  |
| 404 |  | 59 | 12 |  |  |  | 43 | 9.0 |  |  |  | 77 | 12 |  |  |
| 405 |  |  |  | 28 | 22 |  |  |  | 21 | 15 |  |  |  | 24 | 15 |
| 60 mg dose |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 501 |  | 62 | 47 | 34 |  |  | 48 | 32 | 24 |  |  | 254 | 88 | 67 |  |
| 502 |  | 56 | 18 | -12 |  |  | 46 | 14 | -7.0 |  |  | 51 | 13 | 8 |  |
| 503 |  | 70 | 45 | 20 |  |  | 49 | 30 | 12 |  |  | 45 | 54 | 16 |  |
| 504 |  | 71 | 34 | 33 |  |  | 53 | 24 | 22 |  |  | 114 | 39 | 29 |  |

**S4. AEs after start of ORM-12741 treatment (subject count, %)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Preferred term | 0.3 mgN = 2 | 1 mgN = 3 | 10 mgN = 5 | 30 mgN = 5 | 60 mgN = 4 |
| Feeling hot |  |  |  | 1 (20%) |  |
| Sinusitis |  | 1 (33.3%) |  |  |  |
| Gamma-glutamyltransferase increased |  |  |  |  | 1 (25%) |
| Headache | 2 (100%) |  | 2 (40%) | 1 (20%) | 1 (25%) |
| Cough |  | 1 (33.3%) |  |  |  |