### Supplementary table S1: Contribution of external data (ETD or SCD) across different characteristics for the sample of OMs included in marketing authorizations of orphan designated products concluded at the EMA between 2019-2021

| Subset | # of EPAs | # of EPAR | %SCD | %ETD | SCD+ETD in # of EPAR | %SCD+ETD | %no external data in # of EPAR | %no external data | %Trial world post-MA in # of EPAR | % OMAR (MA with SB) | % OMAR | % SCD+ETD in # of OMAR | %ETD | % SCD+ETD | %no external data in # of OMAR | %no external data |
|--------|-----------|-----------|------|------|-----------------------|---------|-------------------------------|----------------|----------------------------------|---------------------|---------|-----------------------|------|---------|-------------------------------|----------------|
| All analysed | 72 | 24 | 33 | 4 | 6 | 18 | 25 | 26 | 36 | 19 | 32 | 46 | 3 | 7 | 13 | 28 | 7 | 15 | 23 | 50 |
| All MA | 66 | 20 | 33 | 4 | 7 | 14 | 23 | 22 | 37 | 3 | 18 | 26 | 24 | 32 | 18 | 28 | 7 | 15 | 23 | 38 |
| MAA withdrawn | 6 | 4 | 44 | 0 | 0 | 3 | 33 | 2 | 22 | NA | NA | NA | NA | NA | NA | NA | NA |
| MAA refused | 3 | 0 | 0 | 0 | 0 | 1 | 33 | 2 | 67 | NA | NA | NA | NA | NA | NA | NA |
| All MA | 2019 | 12 | 5 | 42 | 0 | 0 | 2 | 17 | 5 | 42 | 3 | 25 | 10 | 0 | 0 | 0 | 1 | 10 | 9 | 90 |
| 2020 | 23 | 7 | 30 | 2 | 9 | 5 | 22 | 9 | 39 | 9 | 39 | 20 | 1 | 5 | 5 | 25 | 5 | 25 | 9 | 45 |
| 2021 | 25 | 8 | 32 | 2 | 8 | 28 | 8 | 32 | 7 | 28 | 16 | 2 | 13 | 8 | 5 | 50 | 1 | 6 | 5 | 31 |
| Full MA | 39 | 13 | 33 | 2 | 5 | 5 | 13 | 19 | 49 | 7 | 18 | 12 | 3 | 9 | 7 | 22 | 3 | 9 | 19 | 59 |
| CMA | 17 | 5 | 29 | 2 | 12 | 8 | 47 | 12 | 2 | 8 | 47 | 12 | 0 | 0 | 5 | 42 | 4 | 33 | 3 | 25 |
| ExC | 4 | 2 | 50 | 0 | 0 | 1 | 25 | 1 | 25 | 4 | 100 | 2 | 0 | 0 | 1 | 50 | 0 | 0 | 1 | 50 |
| Prevalence <1 | 31 | 15 | 48 | 1 | 3 | 6 | 19 | 9 | 29 | 14 | 45 | 22 | 1 | 5 | 6 | 27 | 4 | 18 | 11 | 50 |
| Prevalence 1-3 | 14 | 2 | 14 | 0 | 0 | 3 | 21 | 9 | 64 | 1 | 7 | 12 | 1 | 8 | 2 | 17 | 0 | 0 | 9 | 75 |
| Prevalence >3 | 15 | 3 | 20 | 3 | 20 | 5 | 33 | 4 | 27 | 4 | 27 | 12 | 1 | 8 | 5 | 42 | 3 | 25 | 3 | 25 |
| New Active Substance (b) | 51 | 15 | 29 | 4 | 8 | 12 | 24 | 20 | 39 | 19 | 37 | 37 | 1 | 3 | 13 | 35 | 5 | 14 | 18 | 49 |
| Known active substance | 9 | 5 | 56 | 0 | 0 | 2 | 22 | 2 | 22 | 0 | 0 | 9 | 2 | 22 | 0 | 0 | 2 | 22 | 5 | 56 |
| Pivotal study SAT (a) | 24 | 10 | 42 | 1 | 4 | 9 | 38 | 4 | 17 | 12 | 50 | 16 | 0 | 0 | 0 | 3 | 9 | 10 | 4 | 24 |
| Pivotal study RCT (a) | 34 | 10 | 29 | 2 | 6 | 4 | 12 | 18 | 53 | 6 | 18 | 28 | 3 | 3 | 11 | 6 | 21 | 3 | 11 | 16 | 57 |
| Pivotal studies RCT+SAT | 2 | 0 | 0 | 1 | 50 | 1 | 50 | 0 | 0 | 0 | 1 | 50 | 2 | 0 | 0 | 2 | 100 | 0 | 0 | 0 | 0 |
| OD without SB | 13 | 9 | 69 | 0 | 0 | 2 | 15 | 2 | 15 | 6 | 46 | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| OD with SB (c) | 47 | 11 | 23 | 4 | 9 | 12 | 26 | 20 | 43 | 13 | 28 | 46 | 3 | 7 | 13 | 28 | 7 | 15 | 23 | 50 |
| OD maintained at MA | 46 | 17 | 37 | 2 | 4 | 13 | 28 | 14 | 30 | 16 | 35 | 33 | 2 | 6 | 10 | 30 | 7 | 21 | 14 | 42 |
| OD withdrawn at MA | 14 | 3 | 21 | 2 | 14 | 1 | 7 | 8 | 57 | 3 | 21 | 13 | 1 | 8 | 3 | 23 | 0 | 0 | 9 | 69 |
| ATC A | 8 | 0 | 0 | 0 | 0 | 5 | 63 | 3 | 38 | 3 | 38 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 400 |
| ATC B | 7 | 1 | 14 | 0 | 0 | 1 | 14 | 5 | 7 | 2 | 29 | 7 | 1 | 14 | 0 | 0 | 0 | 0 | 0 | 6 66 |
| ATC C,P,R | 3 | 0 | 0 | 0 | 0 | 2 | 67 | 1 | 33 | 0 | 0 | 2 | 0 | 0 | 1 | 50 | 0 | 0 | 1 | 50 |
| ATC C | 3 | 2 | 67 | 0 | 0 | 0 | 3 | 33 | 0 | 0 | 3 | 2 | 67 | 0 | 1 | 33 | 0 | 0 | 2 | 67 |
| ATC J | 3 | 1 | 25 | 0 | 0 | 1 | 25 | 2 | 50 | 2 | 50 | 3 | 0 | 0 | 1 | 33 | 0 | 0 | 2 | 67 |
| ATC L | 27 | 3 | 11 | 4 | 15 | 9 | 33 | 10 | 37 | 3 | 30 | 22 | 0 | 0 | 9 | 41 | 5 | 23 | 8 | 36 |
| ATC M | 3 | 1 | 67 | 0 | 0 | 1 | 33 | 2 | 22 | 0 | 0 | 2 | 67 | 2 | 0 | 0 | 2 | 100 | 0 | 0 | 0 | 0 |
| ATC N | 6 | 5 | 30 | 0 | 0 | 0 | 3 | 30 | 3 | 40 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**ATC:** anatomic therapeutical chemical classification; **CMA:** conditional marketing authorization; **EPAR:** European public assessment report; **ETD:** external trial data, **ExC:** MA under exceptional circumstances; **MA:** marketing authorization; **OM:** orphan designation; **OMAR:** orphan maintenance report.

RCT: randomized clinical trial; SAT: single arm trial; SB: significant benefit; SCD: structured clinical data

(a) One OD with retrospective pivotal data was included in the SAT analysis set.

(b) One OD was classified as new active substance by the EMA, but is known and used outside the EU.

(c) Including one withdrawn OD without OMAR, excluded for analysis in the dataset with n = 46 OMARs.