## Supplemental digital content 1

**The effects of brexpiprazole and aripiprazole on body weight as monotherapy in patients with schizophrenia and as adjunctive treatment in patients with major depressive disorder: an analysis of short- and long-term studies**

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**Supplementary Table 1: Schizophrenia studies included in the analysis**

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| **Study** | **Study design and patients** |
| **Brexpiprazole** | |
| **Short-term** | * Two 6-week, double-blind, placebo-controlled, fixed-dose studies, in adults with schizophrenia:1,2 * Vector (Study 331-10-231; NCT01396421): 0.25 mg/day, 2 mg/day, and 4 mg/day * Beacon (Study 331-10-230; NCT01393613): 1 mg/day, 2 mg/day, and 4 mg/day. * Eligible patients were aged 18–65 years, with a DSM-IV-TR diagnosis of schizophrenia (confirmed by the MINI). They were required to have been experiencing an acute exacerbation of psychotic symptoms, and marked deterioration of usual function (BPRS score ≥40, a score of ≥4 on two or more BPRS items,a and a CGI-S score ≥4), and would have benefitted from hospitalization or continued hospitalization for treatment.1,2 |
| **Long-term** | * Zenith (Study 331-10-237; NCT01397786):b a 52-week, open-label, flexible-dose (1–4 mg/day), extension study for patients completing one of the two short-term, pivotal studies (Vector or Beacon), or the long-term study (Equator), who were willing to discontinue all prohibited psychotropic medications prior to, and during, the study period; *de novo* patients were also included.3 |
| **Aripiprazole** | |
| **Short-term** | * Three 4/6-week, double-blind, placebo-controlled studies, in adults with schizophrenia:4-6 * Kane *et al*., (2002) (4 weeks): aripiprazole 15 mg/day and 30 mg/day; haloperidol 10 mg/day (active control) * Potkin *et al*., (2003) (4 weeks): aripiprazole 20 mg/day and 30 mg/day; risperidone 6 mg/day (active control) * McEvoy *et al*., (2007) (6 weeks): aripiprazole 10 mg/day, 15 mg/day and 20 mg/day. * Eligible patients included men and non-lactating, non-pregnant women, aged 18–65 years (McEvoy *et al*., [2007]: ≥18 years), who had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (McEvoy *et al*., [2007] did not include schizoaffective patients) and who were hospitalized due to an acute relapse.4-6 Eligible patients were also required to have:4-6 * previously shown an improvement with an antipsychotic * been an outpatient for at least one 3-month period during the last year * a PANSS Total score ≥60, with a score ≥4 on at least two items of the psychotic items subscale.c |
| **Long-term** | * Kasper *et al*., (2003): two, 52-week, double-blind, fixed-dose (aripiprazole 30 mg/day; haloperidol 10 mg/day), haloperidol-controlled maintenance studies.7 * The studies were prospectively designed for pooled data evaluation, enrolling patients who had experienced an acute relapse.7 The inclusion criteria were the same as those used in the short-term studies.4-7 |

aHallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness.  
bThe study duration was amended to 26 weeks owing to a sufficient number of patients exposed for >52 weeks.3  
cHallucination, delusion, conceptual disorganization, and suspiciousness/persecution.

BPRS=Brief Psychiatric Rating Scale; CGI-S=Clinical Global Impressions – Severity of illness; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR=DSM-IV, Text Revision; MINI=Mini International Neuropsychiatric Interview; PANSS=Positive and Negative Syndrome Scale.

**Supplementary Table 2: MDD studies included in the analysis**

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| **Study** | **Study design and patients** |
| **Brexpiprazole** | |
| **Short-term** | * Two double-blind, placebo-controlled, fixed-dose studies, in adults with MDD showing an inadequate response to ADT:8,9 * Pyxis (Study 331-10-228; NCT01360645): 2 mg/day as adjunctive treatment to ADT * Polaris (Study 331-10-227; NCT01360632): 1 mg/day and 3 mg/day as adjunctive treatment to ADT. * The studies comprised an 8-week, single-blind prospective treatment phase, followed by a 6-week, double-blind, placebo-controlled, adjunctive treatment phase.8,9 * Eligible patients were outpatients, aged 18–65 years, diagnosed with a single or recurrent nonpsychotic episode of MDD (DSM-IV-TR) lasting ≥8 weeks.8,9 During this episode, patients must have had an inadequate response (<50% improved according to the Massachusetts General Hospital ATRQ) to an adequate trial of 1–3 ADTs.8,9 Patients were also required to have an HDRS-17 Total score ≥18 at screening and at the start of the prospective treatment phase.8,9 |
| **Long-term** | * Study 331-08-212 (NCT01447576): a 52-week, open-label, flexible-dose (0.25–3 mg/day), extension study of brexpiprazole as adjunctive treatment in adults with MDD.10,11 * The study enrolled patients completing either of two parent trials (Study 331-08-211 or Study 331-09-222), plus *de novo* patients.10,11 * Eligible patients were aged 18–65 years, diagnosed with a single or recurrent nonpsychotic episode of MDD (according to DSM-IV-TR criteria and confirmed by the MINI) of duration ≥8 weeks.10 Patients also had to be taking a permitted ADT at an adequate dose for ≥6 weeks by the end of the screening period, and to have reported an inadequate response to at least one, but no more than four, adequate trials of an ADT during the current depressive episode.10 |
| * Orion (Study 331-10-238; NCT01360866):a a 52-week, open-label, flexible-dose (0.5–3 mg/day), extension study of brexpiprazole as adjunctive treatment in adults with MDD.11,12 * The study enrolled patients completing either of the two short-term, pivotal studies (Pyxis or Polaris), or the double-blind, short-term brexpiprazole flexible-dose study, Delphinus (Study 331-10-282).12 Eligible patients had completed participation in the double-blind, randomization phase.12 |

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| **Aripiprazole** | |
| **Short-term** | * Three double-blind, placebo-controlled studies, in adults with MDD – Berman *et al*., (2007), Marcus *et al*., (2008), and Berman *et al*., (2009).13-15 * The studies comprised an 8-week prospective treatment phase, followed by a 6-week, double-blind, adjunctive treatment phase (aripiprazole 2–20 mg/day, or 2–15 mg/day if adjunctive to fluoxetine or paroxetine).13-15 * Eligible patients were outpatients, aged 18–65 years, with a major depressive episode (according to DSM-IV-TR criteria) lasting ≥8 weeks prior to inclusion with an inadequate response (<50% improved according to the Massachusetts General Hospital ATRQ) to at least one, but no more than three, adequate ADT trials of duration ≥6 weeks.13-15 Patients were also required to have an HDRS-17 Total score ≥18 at the end of screening.13-15 |
| **Long-term** | * Berman *et al*., (2011): a 52-week, open-label, flexible-dose (2–30 mg/day if adjunctive to venlafaxine extended-release, escitalopram, mirtazapine or sertraline, or 2–15 mg/day if adjunctive to fluoxetine, paroxetine, duloxetine or bupropion), extension study in adults with MDD.16 * Eligible patients had, previously, completed one of two short-term studies (Berman *et al*., [2007]; Marcus *et al*., [2008]) showing an inadequate response to a prospective ADTb at Week 8, and had completed the 6-week randomized, double-blind period with adjunctive aripiprazole or placebo treatment.16 Patients who were ADT responders at Week 8 of the short-term study were eligible if they did not meet the criteria for remission (MADRS ≤10) at Week 14.16 *De novo* patients were also included.16 |

aThe study was ongoing and the brexpiprazole data presented are based on a cut-off date of 15 May 2015.The study duration was amended to 26 weeks owing to a sufficient number of patients exposed for >52 weeks.11  
bVenlafaxine extended-release, escitalopram, paroxetine controlled-release, fluoxetine or sertraline.

ADT=antidepressant treatment; ATRQ=Antidepressant Treatment Response Questionnaire; DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; HDRS-17=17-item Hamilton Depression Rating Scale; MADRS=Montgomery–Åsberg Depression Rating Scale; MDD=major depressive disorder; MINI=Mini International Neuropsychiatric Interview.

**Supplementary Table 3: Baseline demographics and clinical characteristics in schizophrenia studies**

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|  | **Short-term studies** | | | | | | **Long-term studies** | |
|  | **Brexpiprazole studies** | | | **Aripiprazole studies** | | |
|  | **Placebo (n=368)** | **Brexpiprazole 2 or 4 mg/day (n=732)** | **Placebo (n=317)** | | **Aripiprazole 10, 15, 20 or  30 mg/day (n=718)** | **Brexpiprazole 1–4 mg/day (n=1,072)** | | **Aripiprazole 30 mg/day (n=861)** |
| **Demographics** | | | | | | | | |
| **Age (years), mean (SD)** | 39.5 (10.8) | 39.0 (10.9) | 39.5 (10.5) | | 39.4 (10.6) | 40.0 (11.1) | | 37.3 (11) |
| **Male, n (%)** | 229 (62.2) | 457 (62.4) | 230 (72.6) | | 528 (73.5) | 663 (61.8) | | 511 (59.3) |
| **Weight (kg), mean (SD)** | 77.7 (18.6) | 78.9 (19.6) | 84.2 (20.1)a | | 85.1 (21.6)b | 81.7 (21.0) | | 74.5 (16.3)c |
| **BMI (kg/m2), mean (SD)** | 26.5 (5.5) | 26.9 (6.1) | 28.6 (6.6)a | | 28.7 (7.2)d | 27.9 (6.6) | | 25.5 (5.4)e |
| **Caucasian, n (%)** | 231 (62.8) | 461 (63.0) | 160 (50.5) | | 400 (55.7) | 665 (62.0) | | 733 (85.1) |
| **Clinical characteristics** | | | | | | | | |
| **PANSS Total score, mean (SD)** | 95.3 (12.2)f | 95.6 (12.8)g | 97.6 (18.3) | | 91.5 (18.3)h | 69.5 (17.2)i | | 97.6 (18.3) |
| **CGI-S score, mean (SD)** | 4.9 (0.6) | 4.9 (0.6) | 6.1 (0) | | 6.1 (0)j | 3.5 (0.9)i | | 6.1 (0) |

n=number of patients randomized/enrolled. an=314; bn=712; cn=858; dn=709; en=855; fn=366; gn=728; hn=716; in=1,031; jn=715.

BMI=body mass index; CGI-S=Clinical Global Impressions – Severity of illness; PANSS=Positive and Negative Syndrome Scale; SD=standard deviation.

**Supplementary Table 4: Patient disposition in schizophrenia studies**

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|  | **Short-term studies** | | | | | | **Long-term studies** | |
|  | **Brexpiprazole studies** | | | **Aripiprazole studies** | | |
|  | **Placebo** | **Brexpiprazole 2 or 4 mg/day** | **Placebo** | | **Aripiprazole 10, 15, 20 or 30 mg/day** | **Brexpiprazole 1–4 mg/daya** | | **Aripiprazole 30 mg/day** |
| **Randomized/enrolled** | 368 (100.0) | 732 (100.0) | 317 (100.0) | | 718 (100.0) | 1,072 (100.0) | | 861 (100.0) |
| **Completed** | 227 (61.7) | 504 (68.9) | 162 (51.1) | | 418 (58.2) | 508 (47.4)a | | 367 (42.6) |
| **Discontinued** | 141 (38.3) | 228 (31.1) | 155 (48.9) | | 300 (41.8) | 536 (50.0) | | 494 (57.4) |
| **Withdrew consent** | 42 (11.4) | 103 (14.1) | 46 (14.6) | | 132 (18.4) | 177 (16.5) | | 159 (18.5) |
| **Met withdrawal criteria** | 1 (0.3) | 3 (0.4) | 1 (0.3) | | 3 (0.4) | 81 (7.6) | | 0 (0.0) |
| **Lack of efficacy** | 39 (10.6) | 60 (8.2) | 56 (17.7) | | 85 (11.8) | 43 (4.0) | | 63 (7.3) |
| **Adverse event** | 54 (14.7) | 56 (7.7) | 46 (14.5) | | 62 (8.6) | 159 (14.8) | | 213 (24.7) |
| **Protocol deviation** | 0 (0.0) | 4 (0.5) | 1 (0.3) | | 0 (0.0) | 7 (0.7) | | 8 (0.9) |
| **Withdrawn by investigator** | 4 (1.1) | 2 (0.3) | – | | – | 13 (1.2) | | – |
| **Lost to follow-up** | 1 (0.3) | 0 (0.0) | 1 (0.3) | | 7 (1.0) | 56 (5.2) | | 24 (2.8) |
| **Non-compliance** | – | – | 1 (0.3) | | 7 (1.0) | – | | 25 (2.9) |
| **Study terminated by the Sponsor** | 0 (0.0) | 0 (0.0) | – | | – | 0 (0.0) | | 2 (0.2) |
| **Other** | – | – | 3 (0.9) | | 4 (0.6) | – | | – |

Data presented are n (%).  
a1,044 patients entered the open-label treatment phase.

**Supplementary Table 5: Baseline demographics and clinical characteristics in MDD studies**

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|  | **Short-term, fixed-dose studies** | | | | **Long-term, flexible-dose studies** | | | |
|  | **Brexpiprazole studies** | | **Aripiprazole studies** | |
|  | **ADT + placebo (n=383)** | **ADT + brexpiprazole 1, 2 or  3 mg/day (n=604)** | | **ADT + placebo (n=540)** | | **ADT + aripiprazole 2–15 or  2–20 mg/day (n=550)** | **ADT + brexpiprazole 0.25–3 or  0.5–3 mg/daya (n=2,084)** | **ADT + aripiprazole 2–15 or  2–30 mg/day (n=1,002)** |
| **Demographics** | | | | | | | | |
| **Age (years),  mean (SD)** | 45.7 (11.4) | 44.7 (11.5) | | 44.7 (10.9) | | 45.4 (10.8) | 44.9 (11.4) | 45.7 (11.3) |
| **Male, n (%)** | 123 (32.1) | 188 (31.1) | | 181 (33.5) | | 174 (31.6) | 644 (30.9) | 338 (33.7) |
| **Weight (kg), mean (SD)** | 83.6 (21.0) | 83.9 (20.9) | | 87.6 (22.3)b | | 85.1 (20.4)c | 85.9 (21.2) | 88.5 (22.5)d |
| **BMI (kg/m2), mean (SD)** | 29.5 (7) | 29.7 (6.8) | | 30.8 (7.7)e | | 30.2 (7.1)f | 30.4 (7.1) | 31.2 (7.9)g |
| **Caucasian, n (%)** | 330 (86.2) | 513 (84.9) | | 483 (89.4) | | 484 (88.0) | 1,748 (83.9) | 912 (91.0) |
| **Clinical characteristics** | | | | | | | | |
| **MADRS Total score, mean (SD)** | 26.9 (5.4) | 26.7 (5.5) | | 24.4 (6.1) | | 24.4 (6.1) | 19.4 (8.1) | 18.3 (6.1)h |
| **CGI-S score, mean (SD)** | 4.2 (0.6) | 4.2 (0.6) | | 6.1 (0) | | 6.1 (0) | 3.4 (1.0) | 6.1 (0)h |

n=number of patients randomized/enrolled. aOrion was ongoing; the brexpiprazole data presented are based on a data cut-off date of 15 May 2015.  
bn=533; cn=547; dn=1,001; en=532; fn=545; gn=1,000; hdata are presented for the treated population (n=994).

ADT=antidepressant treatment; BMI=body mass index; CGI-S=Clinical Global Impressions – Severity of illness; MADRS=Montgomery–Åsberg Depression Rating Scale; MDD=major depressive disorder; SD=standard deviation.

**Supplementary Table 6: Patient disposition in MDD studies**

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|  | **Short-term studies** | | | | | **Long-term studies** | | |
|  | **Brexpiprazole studies** | | **Aripiprazole studies** | | |
|  | **ADT + placebo** | **ADT + brexpiprazole 1, 2 or  3 mg/day** | | **ADT + placebo** | **ADT + aripiprazole 2–15 or  2–20 mg/day** | | **ADT + brexpiprazole 0.25–3 or  0.5–3 mg/daya** | **ADT + aripiprazole 2–15 or  2–30 mg/day** |
| **Randomized/enrolled** | 384 (100.0) | 605 (100.0) | | 540 (100.0) | 550 (100.0) | | 2,084 (100.0) | 1,002 (100.0) |
| **Safety population** | 383 (99.7) | 604 (99.8) | | 538 (99.6) | 547 (99.5) | | 2,084 (100.0) | 994 (99.2) |
| **Completed** | 361 (94.0) | 566 (93.6) | | 471 (87.2) | 469 (85.3) | | 1,016 (48.8) | 323 (32.2) |
| **Discontinued** | 23 (6.0) | 39 (6.4) | | 69 (12.8) | 81 (14.7) | | 1,068 (51.2) | 679 (67.8) |
| **Withdrew consent** | 13 (3.4) | 10 (1.7) | | 20 (3.7) | 14 (2.5) | | 281 (13.5) | 125 (12.5) |
| **Met withdrawal criteria** | 3 (0.8) | 5 (0.8) | | – | – | | 88 (4.2) | – |
| **Lack of efficacy** | 0 (0.0) | 1 (0.2) | | 8 (1.5) | 8 (1.5) | | 149 (7.1) | 135 (13.5) |
| **Adverse event** | 2 (0.5) | 15 (2.5) | | 9 (1.7) | 24 (4.4) | | 294 (14.1) | 230 (23.0) |
| **Protocol deviation** | 4 (1.0) | 5 (0.8) | | – | – | | 129 (6.2) | – |
| **Withdrawn by investigator** | 1 (0.3) | 0 (0.0) | | – | – | | 27 (1.3) | – |
| **Lost to follow-up** | 0 (0.0) | 3 (0.5) | | 13 (2.4) | 13 (2.4) | | 100 (4.8) | 109 (10.9) |
| **Non-/poor compliance** | – | – | | 7 (1.3) | 7 (1.3) | | – | 39 (3.9) |
| **No longer meets study criteria** | – | – | | 9 (1.7) | 13 (2.4) | | – | 22 (2.2) |
| **Study terminated by the Sponsor** | 0 (0.0) | 0 (0.0) | | – | – | | – | – |
| **Other** | – | – | | 3 (0.6) | 2 (0.4) | | – | 19 (1.9)b |

Data presented are n (%).  
aOrion was ongoing; the brexpiprazole data presented are based on a data cut-off date of 15 May 2015.  
bIncludes ‘pregnancy’ (n=7; 0.7%) and ‘administrative reason by Sponsor’ (n=2; 0.2%), among other reasons not stated.

ADT=antidepressant treatment; MDD=major depressive disorder.

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