Synopsis – Study 14724B

Study Title Interventional, open-label, flexible-dose extension study of aripiprazole once-monthly in patients with schizophrenia
Investigators 38 principal investigators at 38 sites in 9 countries. *Signatory investigator* – [redacted]
Study Sites 38 sites – 1 in Canada, 6 in Czech Republic, 2 in Estonia, 4 in France, 5 in Germany, 6 in Italy, 5 in Spain, 1 in Sweden, and 8 in United States.
Publications None (as of the date of this report)
Study Period *First patient first visit* – 30 October 2013 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 19 March 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the long-term safety and tolerability of aripiprazole once-monthly (400 or 300 mg/month) in patients with schizophrenia who completed Study 14724A • *Secondary objective*: – to evaluate the effectiveness of aripiprazole once-monthly (400 or 300 mg/month) over a period of 24 weeks in patients with schizophrenia who completed Study 14724A on: - subjective treatment satisfaction - clinical global impression - health-related quality of life • *Pharmacoeconomic objective*: – to evaluate the effects on resource utilization of aripiprazole once-monthly (400 or 300 mg/month) over a period of 24 weeks in patients with schizophrenia who completed Study 14724A

Study Methodology

- This study is an interventional, multi-national, multi-site, open-label, flexible-dose, 28-week extension safety study in patients with schizophrenia who received treatment with aripiprazole once-monthly and completed lead-in Study 14724A.
- A total of 100 eligible patients were planned for enrolment in one treatment group of aripiprazole once-monthly, 400 or 300 mg every month, for a treatment period of 24 weeks and a follow-up period of 4 weeks.
- The study population included men and women aged between 18 and 60 years (extremes included) at the time of entering lead-in Study 14724A, with a DSM-IV-TR™ diagnosis of schizophrenia. Those patients who completed Study 14724A, received aripiprazole once-monthly during the study, were willing to participate in this extension study, fulfilled eligibility criteria for Study 14724B, and were judged to potentially benefit from the 24 weeks treatment with aripiprazole once-monthly according to the clinical opinion of the investigator, were to be enrolled.
- The study consisted of a baseline visit (hereafter referred to as Baseline II), which is the same as Visit 11 (Completion Visit, end of Week 28) of Study 14724A, a 24-week open-label treatment period (once-monthly aripiprazole, 400 or 300 mg), and a 4-week Safety Follow-up Period after completion of the study or after withdrawal from the study.
- At the Baseline II Visit, patients received the first injection of aripiprazole once-monthly 400 or 300 mg. The starting dose in Study 14724B was the same as the last dose received in Study 14724A. However, according to the investigator's judgement the dose could be adjusted if needed; increased to 400 mg for efficacy or decreased to 300 mg for tolerability. In total, patients received 6 injections of aripiprazole once-monthly during the treatment period (1 at the Baseline II Visit, and 1 injection every subsequent 4 weeks).
- Patients were evaluated at the end of Weeks 4, 8, 12, 16, 20, and 24, at which time safety and effectiveness data were collected. All patients were contacted for a safety follow-up assessment 4 weeks after completion/withdrawal.

Number of Patients Planned

100 patients were planned for enrolment.

Diagnosis and Main Selection Criterion

Patients were recruited among those who completed treatment with aripiprazole in lead-in Study 14724A. At entry into the lead-in study, the patients were: outpatients, aged ≥18 and ≤60 years, and diagnosed with schizophrenia according to the DSM-IV-TR™ criteria.

Investigational Medicinal Product, Dose and Mode of Administration, Batch Numbers

Aripiprazole once-monthly – 400 and 300 mg/month; intramuscular (IM) injection; batch No. 2360353, 12K73A400

Duration of Treatment

24 weeks

Effectiveness Assessments

- Quality of Life Scale (QLS)
- Readiness for work questionnaire (WoRQ)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Subjective Well-Being under Neuroleptic Treatment - short version (SWN-S)
- Tolerability and Quality of Life questionnaire (TooL)
- Arizona Sexual Experience Scale (ASEX)

Pharmacoeconomic Assessments

Health Economic Assessment (HEA)

Safety Assessments

Adverse events, clinical safety laboratory tests, vital signs, weight/BMI, waist circumference, electrocardiograms (ECGs), and Columbia-Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoints*:
  - adverse events
  - absolute values and changes from Baseline II in clinical safety laboratory tests, vital signs, weight, and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight, and ECG parameter values
  - C-SSRS categorisation based on C-CASA definitions
- *Secondary endpoints*:
  - change from Baseline II to Week 24 in SWN-S total score
  - change from Baseline II to Week 24 in CGI-S score
  - change from Baseline II to Week 24 in QLS total score and in the 4 QLS domain scores
  - change from Baseline II to Week 24 in TooL total score
  - change from Baseline II to Week 24 in WoRQ total score
  - change from Baseline II to Week 24 in ASEX total score
  - patients categorised as sexually dysfunctional measured at Week 24 on the ASEX scale
  - change from Baseline II to Week 12 in SWN-S total score
  - change from Baseline II to Week 12 in CGI-S score
  - change from Baseline II to Week 12 in QLS total score and in the 4 QLS domain scores
  - change from Baseline II to Week 12 in TooL total score
  - change from Baseline II to Week 12 in WoRQ total score
  - change from Baseline II to Week 12 in ASEX total score
  - patients categorised as sexually dysfunctional measured at Week 12 on the ASEX scale
- *Exploratory endpoints*:
  - change from Baseline I (the baseline visit of Study 14724A) to Week 24 in SWN-S total score
  - change from Baseline I to Week 24 in CGI-S score
  - change from Baseline I to Week 24 in QLS total score
  - change from Baseline I to Week 24 in the 4 QLS domain scores
  - change from Baseline I to Week 24 in TooL total score
  - change from Baseline I to Week 24 in WoRQ total score
  - change from Baseline I to Week 24 in ASEX total score
  - change from Baseline I to Week 12 in SWN-S total score
  - change from Baseline I to Week 12 in CGI-S score
  - change from Baseline I to Week 12 in QLS total score
  - change from Baseline I to Week 12 in the 4 QLS domain scores
  - change from Baseline I to Week 12 in TooL total score
  - change from Baseline I to Week 12 in WoRQ total score
  - change from Baseline I to Week 12 in ASEX total score
- *Pharmacoeconomic endpoints*:
  - number (%) of patients having at least one physician consultation, and average number of consultations per specialty at Week 24 (based on the HEA)
  - number (%) of patients having at least one consultation with other healthcare provider, and average number of consultations per specialty at Week 24 (based on the HEA)
  - number (%) of patients having at least one contact with community-based day services, and average number of contacts per type of day service at Week 24 (based on the HEA)
  - number (%) of patients being hospitalised at least once, and average number of stay and length of stay at Week 24 (based on the HEA)

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who received at least one dose of IMP in Study 14724B
- The change from baseline in total scores related to QLS, WoRQ, SWN-S, TooL, and ASEX, as well as for CGI-S score, are analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model includes region (EU/Non-EU), age group (≤35/>35 years), and visit (all available observations from Baseline II to Week 24 were used) as factors and interaction between baseline value and visit as covariate. An unstructured covariance structure is used to model the within-patient errors. The Kenward-Roger approximation is used to estimate denominator degrees of freedom. The analysis is based on the missing-at-random (MAR) assumption and performed using all available observations (observed cases [OC]) data in the treatment period.
- Adverse events were summarised by the total number and percentage of patients with an adverse event, and the total number of events. Descriptive statistics for the safety variables, both absolute values and changes from baseline, are summarised by visit and for the last assessment.

Patient Disposition and Analysis Sets

- 88 patients were enrolled and treated
- 77 patients (88%) completed the study
- 11 patients withdrew – the reasons for withdrawal were: *adverse event* (5 patients), *withdrawal of consent* (4 patients), *lost to follow-up* (1 patient) and other reason (1 patient).
- 88 patients were analysed in the all-patients-treated-set (APTS)

Demography and Baseline Characteristics of the Study Population

- The mean age of the patients was approximately 43 years (range: 21 to 61 years).
- There were more men (59% [52 patients]) than women (41% [36 patients]).
- At Baseline II, the mean height was 171 cm (range: 143 to 192 cm), the mean weight was 85 kg (range: 51 to 142 kg), the mean BMI was 29 kg/m^2 (range: 18 to 47 kg/m^2), and the mean waist circumference was 98 cm (range: 60 to 131 cm).
- The majority of the patients were White (80%); 19% were Black and 1% were Asian. Nine per cent of the patients reported their ethnicity as Hispanic or Latino.
- Most patients were enrolled in Europe (78% [69 patients]) and 22% (19 patients) were enrolled in North America.

Effectiveness Results

Secondary Endpoints

- Overall, the secondary effectiveness parameters were relatively unchanged or had improved slightly from Baseline II.
- The mean change from Baseline II in QLS total score, based on the MMRM, was 2.3 points at Week 24 and 2.1 points at Week 12. The mean QLS total score at Weeks 24 and 12 was 78.3 and 78.8 points, respectively, and at Baseline II and Baseline I, it was 76.3 and 67.0 points, respectively.
- The mean change from Baseline II in QLS Interpersonal Relations score, based on the APTS, was 0.6 points at Week 24 and 0.7 at Week 12. For QLS Instrumental Role score, the mean change from Baseline II was 0.4 points at Week 24 and 0.0 points at Week 12, and for QLS Intrapsychic Foundations score, it was 0.7 points at Week 24 and 0.7 points at Week 12. The mean change from Baseline II in QLS Common Objects and Activities score, based on the APTS, was 0.2 points at Week 24 and 0.1 points at Week 12.
- The mean change from Baseline II in CGI-S score, based on the MMRM, was -0.1 points at Week 24 and 0.0 points at Week 12.
- The mean change from Baseline II in SWN-S total score, based on the MMRM, was 0.2 points at Week 24 and -1.6 points at Week 12.
- The mean change from Baseline II in TooL total score, based on the MMRM, was -0.5 points at Week 24 and -0.2 points at Week 12.
- The mean change from Baseline II in ASEX total score, based on the MMRM, was -0.4 points at Week 24 and -0.7 points at Week 12. The proportion of patients with sexual dysfunction, based on the ASEX scale, was 35% at Week 24 and 36% at Week 12.

Exploratory Endpoints

- Overall, the exploratory endpoints showed substantial improvements in effectiveness parameters from Baseline I.
- The mean change from Baseline I in QLS total score, based on the MMRM, was 11.5 points at Week 24 and 11.3 points at Week 12.
- The mean change from Baseline I in QLS Interpersonal Relations score, based on the APTS, was 4.5 points at Week 24 and 4.4 points at Week 12. For QLS Instrumental Role score, the mean change from Baseline I in QLS Instrumental Role score was 2.1 points at Week 24 and 1.8 points at Week 12, and for QLS Intrapsychic Foundations score, it was 4.5 points at Week 24 and 4.3 points at Week 12. The mean change from Baseline I in QLS Common Objects and Activities score, based on the APTS, was 0.9 points at Week 24 and 0.8 points at Week 12.
- The mean change from Baseline I in CGI-S score, based on the MMRM, was -1.0 points at Week 24 and -0.9 points at Week 12.
- The mean change from Baseline I in SWN-S total score, based on the MMRM, was 7.6 points at Week 24 and 6.0 points at Week 12.
- The mean change from Baseline I in TooL total score, based on the MMRM, was -2.5 points at Week 24 and -2.2 points at Week 12.
- The mean change from Baseline I in ASEX total score, based on the MMRM, was -3.9 points at Week 24 and -4.3 points at Week 12.

Pharmacoeconomic Results

- Between Baseline II and Week 24, 51% of patients had at least one physician consultation. The most frequently consulted physicians (excluding consultations carried out during the study) were psychiatrists, followed by general practitioners.
- Between Baseline II and Week 24, 26% of patients had at least one consultation with other health care providers. The most frequently consulted other health care providers were social workers, followed by occupational therapist.
- Between Baseline II and Week 24, 22% of patients had at least one contact with community-based day services. The most frequently contacted community-based day services were day care centres, followed by group therapies.
- Between Baseline II and Week 24, 4% of patients (n = 3) were hospitalised at least once. The mean number of hospitalisations was 0.03 per patient.

Safety Results

Primary Endpoint

The adverse event (AE) incidence is summarised below:

	Aripiprazole once-monthly	
	n	(%)
Patients Treated	88	
Patients who died	0	0
Patients with treatment-emergent serious AEs (SAEs)	3	3.4
Patients with treatment-emergent adverse events (TEAEs)	41	46.6
Total number of SAEs	3	
Total number of TEAEs	65	

- The incidence of TEAEs during Study 14724B was 47%.
- The TEAE with the highest incidence during Study 14724B was *weight increased* (7%), followed by *toothache* (3%) and *headache* (3%). The majority of the patients with TEAEs during Study 14724B had TEAEs that were either *mild* or *moderate*. Only 1 patient had 2 TEAEs that were *severe* (*non-cardiac chest pain* and *gastrooesophageal reflux disease*).
- For patients with related TEAEs during Study 14724B, the events were either *mild* or *moderate* (that is, none of the events were *severe*).
- No deaths occurred during Study 14724B. The incidence of SAEs was low (3%). None of the SAEs occurred in >1 patient. None of the SAEs were considered to be related to IMP.
- The only TEAE during Study 14724B that led to withdrawal in ≥2 patients was *weight increased* (n = 2). Both events of *weight increased* were considered to be *probably related* to IMP. *Schizophrenia* and *alcoholism* led to withdrawal in 1 patient each during Study 14724B; both events were considered to be *not related* to IMP. One patient had a lead-in adverse event (*weight increased*) that led to withdrawal, resulting in a total number of 5 patients (6%) withdrawing due to adverse events during Study 14724B.
- No clinically relevant mean changes from Baseline II in clinical safety laboratory test values, vital signs, weight, or ECG values were seen.
- Apart from PCS high S-cholesterol (fasting) (10%), PCS low S-HDL cholesterol (fasting) (7%), and PCS weight increase (7%), the incidences of PCS values during Study 14724B were low (≤5%). A total of 3 patients with PCS laboratory test values during Study 14724B had a corresponding TEAE: *hypercholesterolaemia* (2 patients) and *hypocalcaemia* (1 patient). None of the PCS-related TEAEs were reported as SAEs. Among patients who were withdrawn during Study 14724B due to adverse events, none were withdrawn due to laboratory test values.
- No patients in the study had suicidal behaviour defined as C-SSRS score from 6 to 10. One (1%) patient had suicidal ideation (*wish to be dead*) at 3 occasions during the study.

Conclusions

- Aripiprazole once-monthly (400 or 300 mg/month) was safe and well tolerated in the long-term treatment of adult patients with schizophrenia. The safety profile observed during this extension study was similar to the known safety profile of aripiprazole.
- This extension study also showed a maintenance in improvements in subjective treatment satisfaction, clinical global impression, and health-related quality of life scores that were achieved in Study 14724A (the lead-in study), thereby supporting the use of aripiprazole once-monthly for the long-term treatment of adult patients with schizophrenia.

Report Date

5 October 2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.