Clinical trial results:
European Long-acting Antipsychotics in Schizofrenia Trial EULAST

Summary

EudraCT number	2014-002765-30
Trial protocol	NL AT IT NO BE ES DK HU RO CZ GR
Global end of trial date	26 August 2020

Results information

Result version number	v1 (current)
This version publication date	13 July 2024
First version publication date	13 July 2024

Trial information

Trial identification

Sponsor protocol code	ABR49490

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02146547
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EGRIS Foundation
Sponsor organisation address	Retstraat 13, Beneden-leeuwen, Netherlands, 6658 DB
Public contact	Inge Winter, University Medical Center Utrecht , +31 614674276, i.winter@umcutrecht.nl
Scientific contact	Inge Winter, University Medical Center Utrecht , +31 614674276, i.winter@umcutrecht.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2020
Global end of trial reached?	Yes
Global end of trial date	26 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare all cause discontinuation rates in patients with schizophrenia randomized to oral antipsychotic medications (i.e., aripiprazole or paliperidone) versus depot antipsychotic medications (i.e., paliperidone palmitate or aripiprazole depot) over an 18 month follow-up period.

Protection of trial subjects:

All medication administered in this study is used in clinical practice for the treatment of schizophrenia and schizophreniform disorder in Europe, some longer than others. During the conduct of the EULAST study, potential adverse events were reviewed by the investigator by asking the patient whether they were suffering from adverse events and by the use of the Systematic Monitoring of Adverse events Related to TreatmentS (SMARTS) questionnaire.
The safety of the study was monitored by an independent Data Safety Monitoring Board (DSMB), at a frequency of at least once a year.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 16
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 37
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Austria: 32
Country: Number of subjects enrolled	Belgium: 57
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 61
Country: Number of subjects enrolled	Greece: 24
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	Israel: 116

Worldwide total number of subjects	511
EEA total number of subjects	353

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	509
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at the participating health-care facilities and through public advertisements. Participants were recruited between February 24, 2015, and December 15, 2018.

Pre-assignment

Screening details:

533 patients signed the informed consent and were assessed for eligibility. For 22 patients (4%), data could not be included in the analyses for various reasons. Patients with schizophrenia, aged 18 years or older, having experienced their first psychotic episode six months to seven years before screening, were included.

Period 1

Period 1 title	Assignment and baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Oral antipsychotics

Arm description:

Combined arm of patients who were randomized to aripiprazole oral or paliperidone oral.

Arm type	Active comparator
Investigational medicinal product name	Aripiprazole oral
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The recommended starting dose for aripiprazole is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Investigational medicinal product name	Paliperidone oral
Investigational medicinal product code	
Other name	Invega
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The recommended dose of INVEGA for the treatment of schizophrenia in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 mg to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days.

Arm title	Long Acting Injections

Arm description:

Combined arm of patients who were randomized to aripiprazole depot or paliperidone depot.

Arm type	Active comparator

Investigational medicinal product name	Aripiprazole depot
Investigational medicinal product code	
Other name	Abilify Maintena
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with Abilify Maintena. On the day of initiation, administer one injection of 400 mg Abilify Maintena and continue treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy. After the injection start, the recommended maintenance dose of Abilify Maintena is 400 mg. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection).

Investigational medicinal product name	Paliperidone depot
Investigational medicinal product code	
Other name	Xeplion
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Recommended initiation of Xeplion is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly. The third dose should be administered one month after the second initiation dose. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25 to 150 mg based on individual patient tolerability and/or efficacy.

Number of subjects in period 1	Oral antipsychotics	Long Acting Injections
Started	247	264
Completed	247	264

Baseline characteristics

Reporting groups	
Reporting group title	Oral antipsychotics
Reporting group description:	
Combined arm of patients who were randomized to aripiprazole oral or paliperidone oral.	
Reporting group title	Long Acting Injections
Reporting group description:	
Combined arm of patients who were randomized to aripiprazole depot or paliperidone depot.	

Reporting group values	Oral antipsychotics	Long Acting Injections	Total
Number of subjects	247	264	511
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	245	264	509
From 65-84 years	2	0	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30.8	30.3	
standard deviation	± 10.0	± 9.3	-
Gender categorical Units: Subjects			
Female	75	96	171
Male	172	168	340
Inpatient status Units: Subjects			
Inpatient	130	131	261
Other	117	133	250
PANSS total Units: PANSS total score			
arithmetic mean	74.7	74.1	
standard deviation	± 19.0	± 17.9	-
PANSS Positive subscale Units: PANSS positive subscale			
arithmetic mean	17.5	17.3	
standard deviation	± 6.1	± 5.8	-
PANSS Negative Subscale Units: PANSS negative subscale			
arithmetic mean	20.0	19.8	
standard deviation	± 6.5	± 6.5	-

PANSS General Subscale			
Units: PANSS general subscale			
arithmetic mean	37.2	37.0	
standard deviation	± 9.9	± 9.5	-
CGI Severity			
Units: CGI Severity			
arithmetic mean	4.3	4.4	
standard deviation	± 1.0	± 1.0	-

Subject analysis sets

Subject analysis set title	Intent to treat sample
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.

Reporting group values	Intent to treat sample		
Number of subjects	511		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	509		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	30.5		
standard deviation	± 9.7		
Gender categorical			
Units: Subjects			
Female	171		
Male	340		
Inpatient status			
Units: Subjects			
Inpatient	261		
Other	250		
PANSS total			
Units: PANSS total score			
arithmetic mean	74.3		
standard deviation	± 18.4		
PANSS Positive subscale			
Units: PANSS positive subscale			
arithmetic mean	17.4		
standard deviation	± 6.0		

PANSS Negative Subscale			
Units: PANSS negative subscale			
arithmetic mean	19.9		
standard deviation	± 6.5		
PANSS General Subscale			
Units: PANSS general subscale			
arithmetic mean	37.1		
standard deviation	± 9.7		
CGI Severity			
Units: CGI Severity			
arithmetic mean	4.4		
standard deviation	± 1.0		

End points

End points reporting groups

Reporting group title	Oral antipsychotics
Reporting group description:	
Combined arm of patients who were randomized to aripiprazole oral or paliperidone oral.	
Reporting group title	Long Acting Injections
Reporting group description:	
Combined arm of patients who were randomized to aripiprazole depot or paliperidone depot.	
Subject analysis set title	Intent to treat sample
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Of the patients who signed IC and passed the screening assessments, only those patients are included in the main analyses who have received the study medication.	

Primary: Oral Antipsychotics: 19 months follow-up

End point title	Oral Antipsychotics: 19 months follow-up
End point description:	
End point type	Primary
End point timeframe:	
Patients could meet ACD criteria all throughout the study.	

End point values	Oral antipsychotics	Long Acting Injections	Intent to treat sample	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	247	264	511	
Units: Meeting ACD criteria	175	169	511	

Statistical analyses

Statistical analysis title	Primary and secondary analyses
Statistical analysis description:	
Statistical analyses of primary and secondary outcomes were conducted with SPSS and R. Kaplan-Meier curves were generated using the Survminer (version 0.4.9) R package. Analysis of the primary outcome was performed by ITT using survival analysis, including all randomly allocated participants. For patients who met all-cause discontinuation criteria, the time from randomisation to all-cause discontinuation was used as survival time.	
Comparison groups	Long Acting Injections v Oral antipsychotics v Intent to treat sample

Number of subjects included in analysis	1022
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Kaplan-Meier survival analyses
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.43

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Starting at informed consent, ending 30 days after last study visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Serious adverse events

Reporting group description: -

Serious adverse events	Serious adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 511 (20.16%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Psychiatric disorders			
Psychiatric hospitalisations			
subjects affected / exposed	103 / 511 (20.16%)		
occurrences causally related to treatment / all	16 / 121		
deaths causally related to treatment / all	0 / 2		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Serious adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 511 (16.83%)		
Nervous system disorders			
Akathesia			
subjects affected / exposed	86 / 511 (16.83%)		
occurrences (all)	86		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2014	• changes in Principal Investigators and addition of sites • changes in allowed visit windows • alignment of depot administration with Summary of Product Characteristics • change in cognitive battery (no assessments were conducted at this time)
19 December 2014	• changes in Principal Investigators and addition of sites • a link is created with the EULAST genetics protocol, indicating the purpose of the genetics analyses and the need for a separate informed consent • further specification of timing of assessments • further specification of the timing of discontinuing pre-study antipsychotics • 'Time of first psychosis' (inclusion criteria) is further specified • 'Lost to follow-up' is replaced by 'drop out' in the statistical analyses section as well as the section on the replacement of withdrawn subjects • further specification of the following ACD criterium: medication is switched or augmented with another antipsychotic after visit 4 for more than 1 month (defined as 30 days) continuously OR for more than 3 months (defined as 90 days) cumulative. • a link is created with the EULAST naturalistic follow-up (NFU) protocol, indicating the purpose of the NFU protocol, and the SAE reporting procedure for the NFU is described
13 May 2015	• changes in Principal Investigators and addition of sites • Introduction and Rationale is partly re-written to include recent publications • further specification of the visit windows • guidelines regarding reminding subjects of study visits were added • addition of exclusion criteria concerning parallel participating in another trial • Adjusted of the following exclusion criteria: Patients with a documented history of non-response and/or intolerance to any of the study medications and/or a documented history of non-response to a treatment with one of the study drugs of at least 6 weeks within the registered dose range. Successful past treatment with one of the study drugs is not an exclusion criterion. Based on the SPCs, it is advised not to include patients with severe hepatic illness. • total amount of ml blood to be drawn is reduced • further specification of SAE reporting requirements for the NFU protocol • addition of an SAE reporting requirement for up to 30 days after study medication discontinuation
11 July 2016	• changes in Principal Investigators and addition of sites • lower threshold for the duration of illness is reduced from 1 year to 6 months • inclusion criterium is changed from excluding patients with an intolerance to one of the study drugs to excluding only patients with intolerance to both of the study drugs; if a patient has shown intolerance to one of the study drugs, the patient can still be randomized between the oral and depot arm of the other study drug • augmentation with an antipsychotic qualifies as ACD after a certain amount of days: this now includes the oral version of the study medication • specific Serious Adverse Events are excluded from immediate reporting and instead will be included in the annual line listing • extension of recruitment period

27 November 2018	• changes in Trial Coordinator Central Team and Study Management group, and in Country Coordinators • change in statistical power from 0.9 to 0.8 and a subsequent reduction in the sample size from 150 randomized patients per treatment arms to 130. • extension of recruitment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36716759