Clinical trial results:
A pragmatic randomised double-blind trial of Antipsychotic Treatment of very LAte-onset Schizophrenia-like psychosis: The ATLAS Trial

Summary

EudraCT number	2010-022184-35
Trial protocol	GB
Global end of trial date	14 December 2016

Results information

Result version number	v1 (current)
This version publication date	20 March 2019
First version publication date	20 March 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (ATLAS final Publication - Lancet.pdf)

Trial information

Trial identification

Sponsor protocol code	ATLAS

Additional study identifiers

ISRCTN number	ISRCTN45593573
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Rob Howard, University College London, 0044 20 3549 5114, robert.howard@ucl.ac.uk
Scientific contact	Professor Rob Howard, University College London, 0044 20 3549 5114, robert.howard@ucl.ac.uk
Sponsor organisation name	South London and Maudsley NHS Foundation Trust
Sponsor organisation address	Bethlem Royal Hospital, Monks Orchard Road, Beckenham, London, United Kingdom, BR3 3BX
Public contact	Professor Rob Howard, University College London, 0044 20 3549 5114, robert.howard@ucl.ac.uk
Scientific contact	Professor Rob Howard, University College London, 0044 20 3549 5114, robert.howard@ucl.ac.uk

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	14 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2016
Global end of trial reached?	Yes
Global end of trial date	14 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

(1) Is amisulpride superior to placebo in the treatment of very late-onset schizophrenia-like psychosis over 12 weeks as measured by significant differences between amisulpride and placebo treated groups in improvements in score on the brief psychiatric rating scale (BPRS) largely driven by improvements in the hostility, suspiciousness, hallucinations, tension, uncooperativeness and motor hyperactivity sub-scores?
(2) Is prolonged treatment after 12 weeks superior to treatment withdrawal to receive placebo over the next 12 weeks as measured by significant differences in BPRS scores between groups and significantly greater numbers of patients in the group randomised to receive placebo being withdrawn to open treatment with amisulpride by their physicians?

Protection of trial subjects:

Consent: Although the presence of cognitive impairment was an exclusion criterion for ATLAS, individuals with very late onset schizophrenialike psychosis often have low levels of insight, i.e. they have specific reasoning difficulties
around their self-assessment as patients with an illness that requires treatment. For this reason the clinicians were asked to assess whether the patient is cosidered to have the capacity to give consent prior to doing so.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2012
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	United Kingdom: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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)	0
From 65 to 84 years	71
85 years and over	30

Subject disposition

Recruitment

Recruitment details:

Participants were patients with very late-onset schizophrenia-like psychosis recruited from the community and inpatient teams of UK Old Age Psychiatry services across the UK between 2012 and 2016.

Pre-assignment

Screening details:

i. Diagnosis of very late-onset schizophrenia-like psychosis, including onset of delusions and/or hallucinations after the age of 60 years; and
ii. BPRS score ≥30, or active psychotic symptoms of a nature and severity that would be consistent with a BPRS score of 30 or greater: and
iii. Capacity to give informed consent to inclusion in trial

Pre-assignment period milestones

Number of subjects started	92[1]
Number of subjects completed	92

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 101 patients were randomised, but only 92 patients went on to start trial treatment and hence were included in the ITT analyses

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Trial treatment will be oral amisulpride or identically appearing placebo packed into treatment cartons of 12 weeks' treatment in the form of 3 x 28 blister-packed capsules

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

100mg amisulpride in both stages

Arm type	100mg amisulpride in both stages
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Group A took one capsule containing 100mg amisulpride per day for 24 weeks

Arm title	Arm B

Arm description:

Amisulpride in Stage 1, Placebo in Stage 2

Arm type	Amisulpride then placebo

Investigational medicinal product name	Amisulpride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Group B took one capsule containing 100mg amisulpride per day for 12 weeks, followed by one matched capsule containing placebo per day for a further 12 weeks

Arm title	Arm C

Arm description:

Placebo in Stage 1, Amisulpride in Stage 2

Arm type	Placebo then amisulpride
Investigational medicinal product name	Amisulpride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Group C took one placebo capsule per day for 12 weeks, followed by one capsule containing 100mg amisulpride per day for a further 12 weeks

Number of subjects in period 1[2]	Arm A	Arm B	Arm C
Started	29	32	31
Completed	29	32	31

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 101 patients were randomised, but only 92 patients went on to start trial treatment and hence were included in the ITT analyses

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: 100mg amisulpride in both stages	
Reporting group title	Arm B
Reporting group description: Amisulpride in Stage 1, Placebo in Stage 2	
Reporting group title	Arm C
Reporting group description: Placebo in Stage 1, Amisulpride in Stage 2	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	29	32	31
Age categorical Units: Subjects			
60-69	0	5	0
70-79	13	14	12
> or = 80	16	13	19
Age continuous Units: years			
arithmetic mean	81.2	78.8	80.6
standard deviation	± 6.8	± 8.3	± 5.4
Gender categorical Units: Subjects			
Female	8	7	6
Male	21	25	25
Ethnic Group Units: Subjects			
White	22	22	22
Black	7	7	6
Mixed	0	1	0
Other	0	1	2
Unknown	0	1	1
Home circumstances Units: Subjects			
Living alone	23	20	20
Living with spouse/partner	4	6	6
Other	2	6	5
BPRS score			
Brief Psychiatric Rating Scale			
Units: Subjects			
30-39	11	13	18
40-49	15	12	11
50+	3	7	2
Time with symptoms Units: Subjects			
<6 months	10	3	8

>/= 6 months	17	28	23
Unknown	2	1	0
Antipsychotics			
Taking amisulpride or other antipsychotic drug (now or previously)?			
Units: Subjects			
None previously	13	17	15
Yes, >1 month previously	2	1	6
Yes, in last month	14	14	10
SMMSE score			
Standardised Mini-Mental State Examination			
Units: Subjects			
25-27	15	15	15
28-30	14	17	16
BPRS score			
Brief Psychiatric Rating Scale			
Units: Point			
arithmetic mean	41.4	43.5	38.9
standard deviation	± 7.2	± 9.4	± 6.2
SMMSE score			
Standardised Mini-Mental State Examination			
Units: Point			
arithmetic mean	27.2	27.6	27.8
standard deviation	± 1.5	± 1.6	± 1.7

Reporting group values	Total		
Number of subjects	92		
Age categorical			
Units: Subjects			
60-69	5		
70-79	39		
> or = 80	48		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	21		
Male	71		
Ethnic Group			
Units: Subjects			
White	66		
Black	20		
Mixed	1		
Other	3		
Unknown	2		
Home circumstances			
Units: Subjects			
Living alone	63		
Living with spouse/partner	16		
Other	13		

BPRS score			
Brief Psychiatric Rating Scale			
Units: Subjects			
30-39	42		
40-49	38		
50+	12		
Time with symptoms Units: Subjects			
<6 months	21		
>/= 6 months	68		
Unknown	3		
Antipsychotics			
Taking amisulpride or other antipsychotic drug (now or previously)?			
Units: Subjects			
None previously	45		
Yes, >1 month previously	9		
Yes, in last month	38		
SMMSE score			
Standardised Mini-Mental State Examination			
Units: Subjects			
25-27	45		
28-30	47		
BPRS score			
Brief Psychiatric Rating Scale			
Units: Point arithmetic mean standard deviation	- -		
SMMSE score			
Standardised Mini-Mental State Examination			
Units: Point arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: 100mg amisulpride in both stages	
Reporting group title	Arm B
Reporting group description: Amisulpride in Stage 1, Placebo in Stage 2	
Reporting group title	Arm C
Reporting group description: Placebo in Stage 1, Amisulpride in Stage 2	
Subject analysis set title	Amisulpride in Stage 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving Amisulpride in Stage 1 (i.e. Arms A+B)	
Subject analysis set title	Placebo in Stage 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving Placebo in Stage 1 (i.e. Arm C)	
Subject analysis set title	Amisulpride in Stage 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving Amisulpride in Stage 2 (i.e. Arm A)	
Subject analysis set title	Placebo in Stage 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients receiving Placebo in Stage 2 (i.e. Arm B)	

Primary: Change in BPRS score

End point title	Change in BPRS score
End point description:	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Amisulpride in Stage 1	Placebo in Stage 1	Amisulpride in Stage 2	Placebo in Stage 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	31	19	22
Units: Points				
number (not applicable)	-11.9	-4.2	-1.1	5.2

Statistical analyses

Statistical analysis title	Change in BPRS from Baseline to Week 12
Comparison groups	Amisulpride in Stage 1 v Placebo in Stage 1
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.8
upper limit	11.5

Statistical analysis title	Change in BPRS from Week 12 to final assessment
Comparison groups	Amisulpride in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.024
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	11.7

Primary: Compliance with trial treatment
End point title: Compliance with trial treatment
End point description: No. patients stopping trial treatment
End point type: Primary
End point timeframe: 12 weeks

End point values	Amisulpride in Stage 1	Placebo in Stage 1	Amisulpride in Stage 2	Placebo in Stage 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	61	31	19	22
Units: Subjects	20	13	7	11

Statistical analyses

Statistical analysis title	Compliance with trial treatment
Comparison groups	Amisulpride in Stage 1 v Placebo in Stage 1
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.39
Method	Chi-squared

Statistical analysis title	Compliance with trial treatment
Comparison groups	Amisulpride in Stage 2 v Placebo in Stage 2
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Chi-squared

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From randomisation to final assessment	
Assessment type	Systematic

Dictionary used	
Dictionary name	Trial-specific
Dictionary version	n/a

Reporting groups	
Reporting group title	Arm A
Reporting group description: 100mg amisulpride in both stages	
Reporting group title	Arm B
Reporting group description: Amisulpride in Stage 1, Placebo in Stage 2	
Reporting group title	Arm C
Reporting group description: Placebo in Stage 1, Amisulpride in Stage 2	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Data was not collected on all non-serious adverse events - only those deemed related to trial treatment; number of non-serious adverse events has therefore been reported as zero

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 29 (31.03%)	12 / 32 (37.50%)	7 / 31 (22.58%)
number of deaths (all causes)	0	2	1
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiovascular			
subjects affected / exposed	1 / 29 (3.45%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General disorders and administration site conditions			
Falls			
subjects affected / exposed	1 / 29 (3.45%)	5 / 32 (15.63%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genitourinary			

subjects affected / exposed	1 / 29 (3.45%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other			
subjects affected / exposed	3 / 29 (10.34%)	3 / 32 (9.38%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	1 / 29 (3.45%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Extrapyramidal symptoms			
subjects affected / exposed	1 / 29 (3.45%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric symptoms			
subjects affected / exposed	2 / 29 (6.90%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	2 / 29 (6.90%)	4 / 32 (12.50%)	3 / 31 (9.68%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2012	To clarify/amend 2 eligibility criteria -To amend the IMP labels;
21 March 2013	To change CTA to remove Solian brand of amisulpride and define the IMP by active substance only to allow any brand/generic to be used in the future manufacture of the IMP. Non-substantial changes notified to MHRA with substantial change above: Administrative changes to CTA (add ISRCTN number, update contact details). Correction of error on CTA regarding number of trial arms (changed from 2 to 3). Change in name of manufacturer. . . Removal of 2 sites: Suffolk Mental Health Partnership NHS Trust and Norfolk & Waveney Mental Health NHS Foundation Trust (merged to be become Norfolk & Suffolk NHS Foundation Trust) Change of 2 Pis: Dr. Tabet replacing Dr. Ferrera at Sussex Partnership NHS Foundation Trust; Dr. Fox replacing Dr. Khalifa at Norfolk & Suffolk NHS Foundation Trust.
18 June 2015	Submission of revised IMPD at the next Substantial Amendment, along with the updated MIA(IMP) to reflect the change of name from Bilcare to Sharp. The simplified IMPD submitted with this amendment reflects the fact that bioequivalent generic amisulpride can now be used in the manufacturing process. Documents in the CRF have not been altered, but have been removed from the protocol and appropriately version controlled. The purpose of this amendment is as follows: • To adjust the sample size (N= at least 100) • To add a safety monitoring assessment at Week 16 • To shorten Stg 2 treatment from 24 weeks to 12 weeks • To amend the IMP labels • To clarify the Informed Consent process • To stipulate that the original CRFs should be retained at site and copies returned to the Trial Office • To add visit windows (+/- 1 week) at Week 4 and Week 16 visit • To clarify the SAE reporting process • To revise the Statistics section • To amend the treatment allocation as there will now be a second treatment allocation at the 10-12wk visit
09 November 2015	The protocol has been amended to include an optional blood test at two time points during the trial; once during Stage 1 (ie Week 4 or week 10-12); and once during Stage 2 (Week 16 or Week 22-24). The exclusion criteria have been modified to highlight the optional nature of the blood tests, and the effects of amisulpride on blood levels of amisulpride and the hormone prolactin have been included as secondary efficacy parameters. The results from 20 ATLAS participants will be combined with the dataset obtained from the existing ethically approved trial "Optimisation of Amisulpride prescribing in older people" and the combined dataset will be analysed together. However, this analysis is outside the scope of the ATLAS protocol and the primary and secondary outcomes of the trial remain unchanged.

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/29880238