Clinical trial results:
Clinical Effectiveness Of The Newer Antipsychotic Compounds Olanzapine, Quetiapine And Aripiprazole In Comparison With Low Dose Conventional Antipsychotics (Haloperidol And Flupentixol) In Patients With Schizophrenia

The Neuroleptic Strategy Study - NeSSy

Summary

EudraCT number	2009-010966-47
Trial protocol	DE
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	29 February 2020
First version publication date	29 February 2020

Trial information

Trial identification

Sponsor protocol code	NeSSy_200901

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01164059
WHO universal trial number (UTN)	U1111-1112-9727
Other trial identifiers	DRKS-ID: DRKS00000304

Notes:

Sponsors

Sponsor organisation name	Universität Bremen
Sponsor organisation address	Bibliothekstr. 1, Bremen, Germany, D 28359
Public contact	Prof. Dr. Jürgen Timm Secretary : Kai Baumgarte , Kompetenzzentrum für Klinische Studien Bremen, 0049 421218 63780, timm@uni-bremen.de
Scientific contact	Prof. Dr. Jürgen Timm Secretary : Kai Baumgarte , Kompetenzzentrum für Klinische Studien Bremen, 0049 421218 63780, timm@uni-bremen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	31 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 August 2013
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparing newer and conventional drugs with respect to
contentment with treatment in 1) patients and 2) psychiatrists;
Patient: SF-36 (interviewer version with a time frame of one week); Psychiatrist: CGI.

Protection of trial subjects:

Monitoring of safety laboratory measures, serum level of study drugs, adverse events, metabolic side effects, vital signs. Intervention in case of clinical relevant developments.

Background therapy:

standard of care for psychiatric patients in Germany

Evidence for comparator:

Comparation of typical representatives of newer antipsychotic compounds Olanzapine, Quetiapine, Aripiprazol with typical conventional antipsychotics Haoperidol, Flupentixol.
These representatives were chosen based on practical importance for the therapy of schizophrenia in German hospitals discussed by the leading Germen psychiatries during the planning phase of the study (2008-2009) and agreed on by the international referees.

Actual start date of recruitment	08 April 2010
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	Germany: 149
Worldwide total number of subjects	149
EEA total number of subjects	149

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)	149
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment: first patient in Apri. 8 2010; last patient out August 22, 2013. Recruitment in Germany.

Pre-assignment

Screening details:

Screening criteria: New patients presenting schizophrenia at the acting centers. Check for in/out criteria; screened: 2374, not fulfilling in/out criteria: 1863, denying particiption: 362

Pre-assignment period milestones

Number of subjects started	149
Number of subjects completed	149

Period 1

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

Blinding implementation details:

The study drugs were uniquily capsuled, a neutral parcel with the individual medication for each patient was packed using a random list by a central institute and shipped to the acting centre. The serum level measurement by a special central lab were kept blinded, too. Only in case of danger for the patient an unblinding procedure was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	newer antipsychotics

Arm description:

Treatment with an newer antipsychotic namely one of the compounds olanzapine, quetiapine or aripiprazol

Arm type	Active comparator
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	EU/1/96/022/029
Other name	Zyprexa
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Quetiapine
Investigational medicinal product code	70562.00.00
Other name	Seroquel Prolong
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Aripiprazol
Investigational medicinal product code	EU/1/04/276/001-005
Other name	Abilify
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

5 mg per capsule 2 to 4 capsules p.d.

Arm title	conventional antipsychotics

Arm description:

therapy with conventional antipsychotics, namely haloperidol or flupentixol

Arm type	Active comparator
Investigational medicinal product name	Haloperidol
Investigational medicinal product code	PL 00530/0370
Other name	Serenace
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1,5 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Flupentixol
Investigational medicinal product code	PL 0458/0076
Other name	Fluanxol, Depixol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3 mg per capsule, 2 to 4 capsules p.d.

Number of subjects in period 1	newer antipsychotics	conventional antipsychotics
Started	80	69
Completed	73	63
Not completed	7	6
Protocol deviation	7	6

Period 2

Period 2 title	main trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

The study drugs were uniquily capsuled, a neutral parcel with the individual medication for each patient was packed using a random list by a central institute and shipped to the acting centre. The serum level measurement by a special central lab were kept blinded, too. Only in case of danger for the patient an unblinding procedure was used.

Arms

Are arms mutually exclusive?	Yes

Arm title	newer antipsychotics

Arm description:

Treatment with an newer antipsychotic namely one of the compounds olanzapine, quetiapine or aripiprazol

Arm type	Active comparator
Investigational medicinal product name	Olanzapine
Investigational medicinal product code	EU/1/96/022/029
Other name	Zyprexa
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Quetiapine
Investigational medicinal product code	70562.00.00
Other name	Seroquel Prolong
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Aripiprazol
Investigational medicinal product code	EU/1/04/276/001-005
Other name	Abilify
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5 mg per capsule 2 to 4 capsules p.d.

Arm title	conventional antipsychotics

Arm description:

therapy with conventional antipsychotics, namely haloperidol or flupentixol

Arm type	Active comparator
Investigational medicinal product name	Haloperidol
Investigational medicinal product code	PL 00530/0370
Other name	Serenace
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1,5 mg per capsule, 2 to 4 capsules p.d.

Investigational medicinal product name	Flupentixol
Investigational medicinal product code	PL 0458/0076
Other name	Fluanxol, Depixol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3 mg per capsule, 2 to 4 capsules p.d.

Number of subjects in period 2	newer antipsychotics	conventional antipsychotics
Started	73	63
Completed	21	11
Not completed	52	52
Adverse event, serious fatal	1	-
Adverse event, non-fatal	6	9
Protocol deviation	45	43

Baseline characteristics

Reporting groups	
Reporting group title	newer antipsychotics
Reporting group description:	
Treatment with an newer antipsychotic namely one of the compounds olanzapine, quetiapine or aripiprazol	
Reporting group title	conventional antipsychotics
Reporting group description:	
therapy with conventional antipsychotics, namely haloperidol or flupentixol	

Reporting group values	newer antipsychotics	conventional antipsychotics	Total
Number of subjects	80	69	149
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	34.53	34.43	
standard deviation	± 10.42	± 10.65	-
Gender categorical Units: Subjects			
Female	28	16	44
Male	45	47	92
not in FAS	7	6	13
smoker Units: Subjects			
yes	53	37	90
no	19	24	43
unknown	1	2	3
not in FAS	7	6	13
Duration of illness			
Time since first diagnosis until randomisation			
Units: years			
arithmetic mean	4.86	7.11	
standard deviation	± 5.88	± 7.37	-
SF36			
Total score SF36			
Units: scores			

arithmetic mean	76.92	76.59	
standard deviation	± 13.92	± 16.83	-
BMI			
body mass index			
Units: score			
arithmetic mean	26.39	27.96	
standard deviation	± 6.13	± 7.04	-
CGI-S			
Clinical global impression scale			
Units: Scores			
arithmetic mean	5.10	5.06	
standard deviation	± 0.85	± 0.77	-
PANSS			
Positive and negative syndrom scale			
Units: scores			
arithmetic mean	81.4	83.6	
standard deviation	± 22.8	± 16.9	-

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised patients with at least one drug application

Reporting group values	Full analysis set		
Number of subjects	136		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	34.48		
standard deviation	± 10.53		
Gender categorical			
Units: Subjects			
Female	44		
Male	92		
not in FAS	0		
smoker			
Units: Subjects			
yes	90		

no	43		
unknown	3		
not in FAS	0		
Duration of illness			
Time since first diagnosis until randomisation			
Units: years			
arithmetic mean	5.90		
standard deviation	± 6.61		
SF36			
Total score SF36			
Units: scores			
arithmetic mean	76.77		
standard deviation	± 15.34		
BMI			
body mass index			
Units: score			
arithmetic mean	26.33		
standard deviation	± 6.48		
CGI-S			
Clinical global impression scale			
Units: Scores			
arithmetic mean	5.08		
standard deviation	± 0.81		
PANSS			
Positive and negative syndrom scale			
Units: scores			
arithmetic mean	82.42		
standard deviation	± 20.28		

End points

End points reporting groups

Reporting group title	newer antipsychotics
Reporting group description:	
Treatment with an newer antipsychotic namely one of the compounds olanzapine, quetiapine or aripiprazol	
Reporting group title	conventional antipsychotics
Reporting group description:	
therapy with conventional antipsychotics, namely haloperidol or flupentixol	
Reporting group title	newer antipsychotics
Reporting group description:	
Treatment with an newer antipsychotic namely one of the compounds olanzapine, quetiapine or aripiprazol	
Reporting group title	conventional antipsychotics
Reporting group description:	
therapy with conventional antipsychotics, namely haloperidol or flupentixol	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients with at least one drug application	

Primary: SF36 AUC

End point title	SF36 AUC
End point description:	
Area under curve of SF36 values with log-time scale.	
End point type	Primary
End point timeframe:	
during main period	

End point values	newer antipsychotics	conventional antipsychotics		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[1]	60[2]		
Units: Scores				
arithmetic mean (standard deviation)	85.1 (± 14.7)	79.8 (± 17.2)		

Notes:

[1] - 6 cases of full analysis set not assessable

[2] - 3 cases of full analysis set not assessable

Attachments (see zip file)	SF36 values baseline corrected (%)/SF36 development.pptx

Statistical analyses

Statistical analysis title	SF36 ANCOVA
Statistical analysis description:	
Testing contrast for both groups after ANCOVA with all 5 drugs as factors.	
Comparison groups	newer antipsychotics v conventional antipsychotics

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118 [3]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	8
Variability estimate	Standard deviation
Dispersion value	15.4

Notes:

[3] - A 5% Bonferroni-Holm procedure was applied and p<0.025 is significant.

Primary: CGI AUC

End point title	CGI AUC

End point description:

Area under curve of CGI values on logtime scale

End point type	Primary

End point timeframe:

during main trial period

End point values	newer antipsychotics	conventional antipsychotics		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	63		
Units: Score				
arithmetic mean (standard deviation)	3.26 (± 0.92)	3.38 (± 0.88)		

Attachments (see zip file)	CGI development/CGI development.pptx

Statistical analyses

Statistical analysis title	CGI ANCOVA

Statistical analysis description:

Testing contrast of comparison groups with ANCOVA involving all 5 drugs as factors

Comparison groups	newer antipsychotics v conventional antipsychotics

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3701 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.08
Variability estimate	Standard deviation
Dispersion value	0.9

Notes:

[4] - A 5% Bonferroni-Holm procedure was applied. p>0.025 is not significant (preplanned analysis). Due to deviation from normality a sensitvty analysis with Mann-Whitney-test was conducted. Result: P=0.3037 confirming the non significant result.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: main trial period	
Adverse event reporting additional description: questionaire at each of 6 visits (week 1,2,4,6,12,24)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Newer compounds
Reporting group description: -	
Reporting group title	conventional compounds
Reporting group description: -	

Serious adverse events	Newer compounds	conventional compounds	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 73 (13.70%)	6 / 63 (9.52%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
suspected drug misuse	Additional description: death; same patient tried suicide about 2 months ago. She was at home 2 months after last application of study medication.		
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
sleepless, angst	Additional description: increasing angst, sleepless, restiveness		
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
pneumonia; lung embolism			
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suizidversuch, Suizidgedanken			
subjects affected / exposed	2 / 73 (2.74%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
psychotische Decompensation, Exazerbation, emotionaler Einbruch etcerb	Additional description: combination of SAEs with varying descriptions		
subjects affected / exposed	7 / 73 (9.59%)	6 / 63 (9.52%)	
occurrences causally related to treatment / all	1 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Newer compounds	conventional compounds	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 73 (43.84%)	24 / 63 (38.10%)	
General disorders and administration site conditions			
General physical condition decreased			
subjects affected / exposed	5 / 73 (6.85%)	3 / 63 (4.76%)	
occurrences (all)	5	3	
Reproductive system and breast disorders			
Libido decreased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	1 / 73 (1.37%)	0 / 63 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Psychiatric evaluation abnormal subjects affected / exposed occurrences (all)	6 / 73 (8.22%) 6	3 / 63 (4.76%) 3	
Cardiac disorders Cardiac disorder subjects affected / exposed occurrences (all)	3 / 73 (4.11%) 3	1 / 63 (1.59%) 1	
Nervous system disorders Nervous system disorder subjects affected / exposed occurrences (all)	18 / 73 (24.66%) 18	18 / 63 (28.57%) 18	
Eye disorders Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	1 / 63 (1.59%) 1	
Gastrointestinal disorders Gastric disorder subjects affected / exposed occurrences (all)	6 / 73 (8.22%) 6	6 / 63 (9.52%) 6	
Hepatobiliary disorders Hepatitis C subjects affected / exposed occurrences (all)	1 / 73 (1.37%) 1	0 / 63 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all)	5 / 73 (6.85%) 5	0 / 63 (0.00%) 0	
Renal and urinary disorders Renal disorder subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	1 / 63 (1.59%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal disorder subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	2 / 63 (3.17%) 2	
Metabolism and nutrition disorders Metabolic disorder			

subjects affected / exposed occurrences (all)	2 / 73 (2.74%) 2	2 / 63 (3.17%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2012	Update of known adverse reactions in "Fchinformation" of study drugs
03 November 2012	Update of known adverse reactions in "Fchinformation" of study drugs; expanding inclusion of Patient with less then 1 year but more than 6 months duration of illness
05 December 2012	Update of known adverse reactions in "Fchinformation" of study drugs; update of manufacturing process of placebo

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported