Clinical trial results:
ADS-5102 (Amantadine HCl) Extended Release Efficacy and Safety Study in Parkinson's Disease Patients with Levodopa-Induced Dyskinesia

Summary

EudraCT number	2014-003738-24
Trial protocol	DE ES AT
Global end of trial date	10 March 2016

Results information

Result version number	v1 (current)
This version publication date	25 March 2017
First version publication date	25 March 2017

Trial information

Trial identification

Sponsor protocol code	ADS-AMT-PD304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02136914
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Adamas Pharmaceuticals, Inc
Sponsor organisation address	1900 Powell Street, Suite 750, Emeryville, United States, CA94608
Public contact	Clinical Trials Information, Adamas Pharmaceuticals, Inc., +1 5104503500, RegistroEspanolDeEstudiosClinicos@druginfo.com
Scientific contact	Clinical Trials Information, Adamas Pharmaceuticals, Inc., +1 5104503500, RegistroEspanolDeEstudiosClinicos@druginfo.com

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	12 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2016
Global end of trial reached?	Yes
Global end of trial date	10 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ADS-5102 oral capsules, an extended release formulation of amantadine, at a dose level of 340 mg, dosed once nightly at bedtime for 13 weeks, for the treatment of levodopa-induced dyskinesia (LID) in subjects with Parkinson's disease (PD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to International Council for Harmonisation Guidelines.

Background therapy:

For at least 30 days prior to Screening and throughout participation in the study, subjects were to receive stable doses and regimens of antiparkinson medications, including any levodopa preparation administered at least 3 times daily.

Evidence for comparator: -

Actual start date of recruitment	23 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	77
EEA total number of subjects	52

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)	31
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who provided written informed consent and met all eligibility criteria were randomly assigned in a 1:1 ratio to receive either placebo or ADS-5102 (340mg).

Pre-assignment

Screening details:

Male and female subjects between 30 and 85 years of age, inclusive; had PD per the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria; were ambulatory or ambulatory aided (walker or cane) while ON (the time during which PD symptoms were adequately controlled) and could complete study assignments were selected per protocol.

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, Data analyst, Assessor

Blinding implementation details:

Study drug was administered in a double blind fashion. Placebo capsules were indistinguishable in size and appearance from ADS-5102 capsules. A subject's treatment assignment was only to be unblinded when knowledge of the treatment was essential to the safety of the patient. The investigator was responsible for ensuring that instructions for unblinding were stored safely, the location known and readily available to the relevant staff if required. No emergency unblinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	ADS-5102

Arm description:

Active treatment group

Arm type	Experimental
Investigational medicinal product name	ADS-5102
Investigational medicinal product code	ADS-5102
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

ADS-5102 was taken once daily at bedtime (if possible, no earlier than 9pm). The ADS-5102 dose was 170 mg during week 1 (1 ADS-5102 capsule and 1 placebo capsule), 340 mg during Weeks 2 through 12 (2 ADS-5102 capsules) and 170 mg during Week 13 (1 ADS-5102 capsule and 1 placebo capsule). Capsules were to be swallowed intact with any non-alcoholic beverage with or without food.

Arm title	Placebo

Arm description:

Placebo group

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo was taken once daily at bedtime (if possible, no earlier than 9pm) and consisted of 2 placebo capsules Weeks 1 through 13. Capsules were to be swallowed intact with any non-alcoholic beverage with or without food.

Number of subjects in period 1[1]	ADS-5102	Placebo
Started	37	38
Completed	29	35
Not completed	8	3
Unwilling to proceed	1	-
Consent withdrawn by subject	6	3
Adverse event, non-fatal	1	-

Notes:

[1] - 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: 77 Subjects were enrolled worldwide but 2 Subjects were randomized in error and did not receive study medication. One Subject was randomized to placebo and one was randomized to active. Results are reported for the 75 Subjects who received at least one dose of study medication.

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial (overall period)

Reporting group description: -

Reporting group values	Overall Trial (overall period)	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	44	44	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	64.8		
standard deviation	± 9.31	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	39	39	

Subject analysis sets

Subject analysis set title	Modified Intent to Treat (MITT) ADS-5102
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The MITT population included all randomized subjects who were dosed and provided at least 1 post-baseline assessment of UDysRS (Unified Dyskinesia Rating Scale). The MITT population was used for the primary analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects were included in the treatment group to which they were randomized.

Subject analysis set title	Modified Intent to Treat (MITT) Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The MITT population included all randomized subjects who were dosed and provided at least 1 post-baseline assessment of UDysRS (Unified Dyskinesia Rating Scale). The MITT population was used for the primary analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects were included in the treatment group to which they were randomized.

Subject analysis set title	Safety Population ADS-5102
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomized subjects who received at least 1 dose of study drug. The safety population was used for safety analyses. In these analyses, subjects were analysed according to the treatment received most often.

Subject analysis set title	Safety population - placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all randomized subjects who received at least 1 dose of study drug. The safety population was used for safety analyses. In these analyses, subjects were analysed according to the treatment received most often.

Reporting group values	Modified Intent to Treat (MITT) ADS-5102	Modified Intent to Treat (MITT) Placebo	Safety Population ADS-5102
Number of subjects	37	38	37
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)	16	15	16
From 65-84 years	21	23	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.7	64.9	64.7
standard deviation	± 9.66	± 9.08	± 9.66
Gender categorical Units: Subjects			
Female	18	18	18
Male	19	20	19

Reporting group values	Safety population - placebo		
Number of subjects	38		
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)	15		
From 65-84 years	23		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	64.9		
standard deviation	± 9.08		
Gender categorical Units: Subjects			
Female	18		
Male	20		

End points

End points reporting groups

Reporting group title	ADS-5102
Reporting group description:	
Active treatment group	
Reporting group title	Placebo
Reporting group description:	
Placebo group	
Subject analysis set title	Modified Intent to Treat (MITT) ADS-5102
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The MITT population included all randomized subjects who were dosed and provided at least 1 post-baseline assessment of UDysRS (Unified Dyskinesia Rating Scale). The MITT population was used for the primary analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects were included in the treatment group to which they were randomized.	
Subject analysis set title	Modified Intent to Treat (MITT) Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The MITT population included all randomized subjects who were dosed and provided at least 1 post-baseline assessment of UDysRS (Unified Dyskinesia Rating Scale). The MITT population was used for the primary analysis, as well as for all secondary efficacy analyses. In all analyses and summaries based on the MITT population, subjects were included in the treatment group to which they were randomized.	
Subject analysis set title	Safety Population ADS-5102
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized subjects who received at least 1 dose of study drug. The safety population was used for safety analyses. In these analyses, subjects were analysed according to the treatment received most often.	
Subject analysis set title	Safety population - placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included all randomized subjects who received at least 1 dose of study drug. The safety population was used for safety analyses. In these analyses, subjects were analysed according to the treatment received most often.	

Primary: Change from Baseline in UDysRS Total Score at Week 12 (MITT population)

End point title	Change from Baseline in UDysRS Total Score at Week 12 (MITT population)
End point description:	
The UDysRS is a 26-item rating scale which evaluates involuntary movements often associated with treated Parkinson's Disease. The scale has four parts with a total possible score of 104.	
End point type	Primary
End point timeframe:	
Week 12	

End point values	Modified Intent to Treat (MITT) ADS-5102	Modified Intent to Treat (MITT) Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Total Score				
arithmetic mean (standard deviation)				
Baseline	41.7 (± 12.57)	40.4 (± 10.09)		
Week 12	20.8 (± 11.83)	33.3 (± 14.35)		
Change from Baseline	-21 (± 16.6)	-7.1 (± 12.14)		

Statistical analyses

Statistical analysis title	MMRM Treatment Difference (Active-Placebo)

Statistical analysis description:

The mixed model with repeat measures (MMRM) included all categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate. The dependent variable was the change from baseline. MMRM Least squares (standard error) mean change from baseline at Week 12 were calculated. Summary statistics were computed using data for subjects who had values at both baseline and Week 12.

Comparison groups	Modified Intent to Treat (MITT) ADS-5102 v Modified Intent to Treat (MITT) Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	LS mean treatment difference
Point estimate	-14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.4
upper limit	-8.3
Variability estimate	Standard error of the mean
Dispersion value	3.03

Secondary: Change from Baseline in PD Diary ON Time Without Troublesome Dyskinesia at Week 12 (MITT Population)

End point title	Change from Baseline in PD Diary ON Time Without Troublesome Dyskinesia at Week 12 (MITT Population)

End point description:

Patient reported diary state where ON time without troublesome dyskinesia is the duration of time that a patient is free from troublesome dyskinesia.

End point type	Secondary

End point timeframe:

Week 12

End point values	Modified Intent to Treat (MITT) ADS-5102	Modified Intent to Treat (MITT) Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Hours				
arithmetic mean (standard deviation)	9.14 (± 2.388)	7.64 (± 3.234)		

Statistical analyses

Statistical analysis title	MMRM Treatment Difference (Active - Placebo)

Statistical analysis description:

The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate. Summary statistics were computed using data from subjects who had values at both baseline and Week 12.

Comparison groups	Modified Intent to Treat (MITT) ADS-5102 v Modified Intent to Treat (MITT) Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0168
Method	MMRM
Parameter estimate	LS mean treatment difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	3.45
Variability estimate	Standard error of the mean
Dispersion value	0.775

Secondary: Change from Baseline to Week 12 in PD Diary OFF time

End point title	Change from Baseline to Week 12 in PD Diary OFF time

End point description:

OFF time refers to the duration of time when a patient is not benefiting from medication.

End point type	Secondary

End point timeframe:

Week 12

End point values	Modified Intent to Treat (MITT) ADS-5102	Modified Intent to Treat (MITT) Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Hours				
arithmetic mean (standard deviation)	2.76 (± 2.104)	1.95 (± 1.687)		

Statistical analyses

Statistical analysis title	MMRM Treatment Difference (Active - Placebo)

Statistical analysis description:

The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate. Summary statistics were computed using data from subjects who had values at both baseline and Week 12.

Comparison groups	Modified Intent to Treat (MITT) ADS-5102 v Modified Intent to Treat (MITT) Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0199
Method	MMRM
Parameter estimate	LS mean treatment difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.461

Secondary: Overview of Adverse Events

End point title	Overview of Adverse Events

End point description:

Overview of Adverse Events (Safety Population)

End point type	Secondary

End point timeframe:

From start of study medication (all AEs collected were treatment-emergent) to final follow-up assessment.

End point values	Safety Population ADS-5102	Safety population - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	38		
Units: Subjects				
Subjects with any AEs	31	19		
Subjects with study drug related AEs	21	10		
Subjects with Serious AEs	4	0		
Subjects with study drug related SAEs	1	0		
Subjects who discontinued due to AE	7	3		
Discontinued due to study drug related AEs	6	2		
Subjects with any AEs highest intensity MILD	8	12		
Subjects with any AEs highest intensity MODERATE	18	5		
Subjects with any AEs highest intensity SEVERE	5	2		
Subjects with related AEs highest intensity MILD	5	7		
Subjects with related AEs highest intensity MOD.	12	2		
Subjects with related AEs highest intensity SEVERE	4	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event with an onset date after study drug administration up to and including the designated Safety Follow-up Visit.

Adverse event reporting additional description:

Adverse events are reported as one occurrence for each event reported.

Non-serious adverse events:
Most common AEs (at least 5% of subjects in the active treatment group) are reported.
Total subjects affected by non-serious AEs refers to the number of subjects with any AEs experienced by >=5% of subjects in the active treatment group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Safety Population ADS-5102
Reporting group description: -	
Reporting group title	Safety Population Placebo

Reporting group description: -

Serious adverse events	Safety Population ADS-5102	Safety Population Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 37 (10.81%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiorespiratory arrest			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysesthesia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 37 (2.70%)	0 / 38 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Population ADS-5102	Safety Population Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 37 (83.78%)	19 / 38 (50.00%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 37 (8.11%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
Vascular disorders			

Orthostatic hypotension			
subjects affected / exposed	4 / 37 (10.81%)	0 / 38 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
Dystonia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	2 / 37 (5.41%)	1 / 38 (2.63%)	
occurrences (all)	2	1	
Somnolence			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	5 / 37 (13.51%)	1 / 38 (2.63%)	
occurrences (all)	5	1	
Nausea			
subjects affected / exposed	5 / 37 (13.51%)	1 / 38 (2.63%)	
occurrences (all)	5	1	
Constipation			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 37 (10.81%)	0 / 38 (0.00%)	
occurrences (all)	4	0	
Hallucination (Pooled)	Additional description: The "Hallucinations (Pooled)" term combines all PTs that contain the term "Hallucination" and in this case combines "Hallucination, visual" and "Hallucination, auditory".		
subjects affected / exposed	3 / 37 (8.11%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
Apathy			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Depressed Mood			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Hallucination, visual			
subjects affected / exposed	3 / 37 (8.11%)	2 / 38 (5.26%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 37 (5.41%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 37 (5.41%)	3 / 38 (7.89%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 37 (10.81%)	0 / 38 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2014	Amendment 1. To the exclusion criterion regarding sexually active females, simplified the wording regarding acceptable contraception and specified that a hormonal method was to used in combination with a barrier method. Added that subjects with untreated angle closure glaucoma would be excluded from the study. Added that subjects with suicidal ideation and subjects with a history of suicidal ideation or suicide attempt during amantadine treatment would be excluded from the study. Added that use of medications that prolonged the QT interval and had a known risk of torsades de pointes would exclude a subject from the study unless the medication was discontinued at least 60 days prior to Screening. Added (to the appendix of prohibited medications) a list of agents that prolong the QT interval and had a known risk of torsades de pointes. Added urine pregnancy testing for female subjects of childbearing potential at the end of Weeks 4, 8, 12 and 18; modified the schedule of assessments accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported