EU Clinical Trials Register

Clinical trial results:
A randomized, double blind, placebo controlled trial to evaluate the safety and efficacy of Apovir for treatment of patients with Alzheimer's disease

Summary

EudraCT number	2013-002126-23
Trial protocol	SE
Global end of trial date	23 June 2016

Results information

Result version number	v1 (current)
This version publication date	08 July 2017
First version publication date	08 July 2017

Trial information

Trial identification

Sponsor protocol code	APOCT-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Apodemus AB
Sponsor organisation address	Nobels väg 2, Solna, Sweden, 171 65
Public contact	Clinical trials, Apodemus AB, 46 708 681368, info@apodemus.se
Scientific contact	Clinical trials, Apodemus AB, 46 708 681368, info@apodemus.se

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	23 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2016
Global end of trial reached?	Yes
Global end of trial date	23 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main efficacy objective: To investigate the effect of Apovir on disease progression of Alzheimer's Disease as assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-cog] compared to placebo. The change in score Before and after 9 months of treatment with Apovir or placebo respectively was assessed.

Main safety objective: To investigate the safety and tolerability of the combination therapy of Apovir in patients with AD

Protection of trial subjects:

The trial was in compliance with the ethical principles derived from the Declaration of Helsinki, the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local regulatory requirements.

Background therapy:

Acethylcholinesterase inhibitor or memantine

Evidence for comparator:

-

Actual start date of recruitment	28 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	6
From 65 to 84 years	61
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were recruited via advertising in local newspaper and via medical record searches at memory clinics in the Stockholm area. Patients were prescreened for main eligibility criteria by the Clinical trial site personnel before a screening visit was scheduled.

Pre-assignment

Screening details:

Eligible patients were 60-85 years old, had an Alzheimer's Disease diagnosis and a MMSE score 27-21. Patients could be on treatment with other Alzheimer's Disease medication (acetylcholinesterase inhibitors or memantine) if drug and dose had been stable for at least 3 months prior to inclusion. Out of 169 patients screened 69 were randomized.

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, Data analyst, Carer, Assessor

Blinding implementation details:

All patients and study staff were blinded during the entire trial. DSMB received unblinded safety data during the safety reporting period of the trial. From 2015-04-21 and onwards, the Sponsor CEO was given access to unblinded data required for strategic decisions. In order to minimize bias, the Sponsor CEO was from this time-point not involved in any discussions or decisions regarding individual patients e.g. participation in the Clean file meeting was not allowed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apovir

Arm description:

Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant.
Patients randomised to Apovir before first administration of IMP.

Arm type	Experimental
Investigational medicinal product name	APO-P001
Investigational medicinal product code	
Other name	pleconaril, picovir
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

 APO-P001 600 mg/day (200 mg in the morning and 400 mg in the evening) was to be taken by the patients Daily for 9 months. IMP was to be taken together with food.

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

Dosage and administration details:

Ribavirin was to be taken twice daily in the morning and in the evening for 9 months. The daily dose, 600 mg was decreased for all patients to 400 mg during the trial. Ribavirin was to be taken together with food.

Arm title	Placebo

Arm description:

Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant.
Patients randomised to placebo before first administration of IMP.

Arm type	Placebo
Investigational medicinal product name	Placebo APO-P001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo APO-P001 capsules were to be taken in the same manner as the Apovir APO-P001 capsules.

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

Dosage and administration details:

Ribavirin placebo capsules were to be taken in the same manner as the Apovir ribavirin capsules.

Number of subjects in period 1	Apovir	Placebo
Started	35	34
Completed	35	34

Period 2

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

Blinding implementation details:

All patients and study staff were blinded during the entire trial. DSMB received unblinded safety data during the safety reporting period of the trial. From 2015-04-21 and onwards, the Sponsor CEO was given access to unblinded data required for strategic decisions. In order to minimize bias, the Sponsor CEO was from this time-point not involved in any discussions or decisions regarding individual patients e.g. participation in the Clean file meeting was not allowed.

Arms

Are arms mutually exclusive?	Yes

Arm title	Apovir

Arm description:

Patients randomised to Apovir, a combination of APO-P001 and ribavirin. Apovir was taken orally, together with food twice Daily for 9 months. A daily dose of 600 mg APO-P001 and 600 mg ribavirin (decreased to 400 mg for all patients during the trial) were administered by the patients at home.

Arm type	Experimental
Investigational medicinal product name	APO-P001
Investigational medicinal product code	
Other name	pleconaril, picovir
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

 APO-P001 600 mg/day (200 mg in the morning and 400 mg in the evening) was to be taken by the patients Daily for 9 months. IMP was to be taken together with food.

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

Dosage and administration details:

Ribavirin was to be taken twice daily in the morning and in the evening for 9 months. The daily dose, 600 mg was decreased for all patients to 400 mg during the trial. Ribavirin was to be taken together with food.

Arm title	Placebo

Arm description:

Patints randomised to placebo. Placebo capsules for APO-P001 and ribavirin respectively were administered twice Daily for 9 months in the same manner as the Apovir capsules.

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

Dosage and administration details:

Ribavirin placebo capsules were to be taken in the same manner as the Apovir ribavirin capsules.

Investigational medicinal product name	Placebo APO-P001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo APO-P001 capsules were to be taken in the same manner as the Apovir APO-P001 capsules.

Number of subjects in period 2	Apovir	Placebo
Started	35	34
Completed	17	30
Not completed	18	4
Adverse event, serious fatal	1	-

Patient discontinued treatment	1	-
Consent withdrawn by subject	4	1
Adverse event, non-fatal	10	3
Hb lower than 105 g/L for women and 110 g/L for me	1	-
Patient relative got sick	1	-

Period 3

Period 3 title	Long-term follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Patients and site staff remained blinded throughout the entire trial. From 2015-04-21 and onwards, the Sponsor CEO was given access to unblinded data required for strategic decisions. The CRO, including statistician and other Sponsor associates were unblinded after the first clean file meeting held on the 16SEP2015. At this time-point all patients had completed the 1 month post treatment follow-up visit. 35 visits were still to be performed at this time-point.

Arms

Are arms mutually exclusive?	Yes
Arm title	Apovir

Arm description:

Patients randomised to Apovir. Follow-up period assessing effect of treatment 6 and 12 months after end of treatment in the Apovir treatment Group.

Arm type	Experimental
Investigational medicinal product name	APO-P001
Investigational medicinal product code	
Other name	pleconaril, picovir
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

This is the post treatment follow-up period of the trial, IMP was not adminsitered.

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

Dosage and administration details:

This is the post treatment follow-up period of the trial, IMP was not adminsitered.

Arm title	Placebo

Arm description:

Patients randomised to Placebo. Follow-up period assessing effect of treatment 6 and 12 months after end of treatment in the Placebo treatment Group.

Arm type	Placebo

Investigational medicinal product name	Placebo APO-P001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

This is the post treatment follow-up period of the trial, IMP was not adminsitered.

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

Dosage and administration details:

This is the post treatment follow-up period of the trial, IMP was not adminsitered.

Number of subjects in period 3[1]	Apovir	Placebo
Started	13	28
Completed	12	25
Not completed	1	3
Lost to follow-up	1	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All patients who completed the 1 month follow-up visit were invited to take part in the follow-up part of the trial both subjects who were included in the PPAS and those who were only included in the FAS.

Baseline characteristics

Reporting groups

Reporting group title	Apovir
Reporting group description:	
Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant. Patients randomised to Apovir before first administration of IMP.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant. Patients randomised to placebo before first administration of IMP.	

Reporting group values	Apovir	Placebo	Total
Number of subjects	35	34	69
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)	2	4	6
From 65-84 years	32	29	61
85 years and over	1	1	2
Age continuous			
Units: years			
arithmetic mean	73.8	71.7	
standard deviation	± 5.3	± 5.9	-
Gender categorical			
Units: Subjects			
Female	19	15	34
Male	16	19	35
Ethnic origin			
Units: Subjects			
Caucasian	35	34	69
African descent	0	0	0
Asian or Pacific Islander	0	0	0
Mixed / Multi-racial	0	0	0
Other	0	0	0
Any medical/Surgical history			
Units: Subjects			
Medical/Surgical history reported	17	22	39
No medical/Surgical history reported	18	12	30

Any concurrent disease Units: Subjects			
Concurrent disease reported	35	34	69
No concurrent disease reported	0	0	0

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set was defined as all patients who received at least one dose of the IMP. Patients were analysed as treated.

Subject analysis set title	Full analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The FAS is defined as all randomised patients who received at least 1 dose of the IMP and have at least 1 post-baseline assessment of efficacy data. In analyses performed on the FAS, patients have been analysed as randomised.

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The PPAS is a subset of the FAS fulfilling the following additional criteria:
1.   All important inclusion criteria and none of the important exclusion criteria were fulfilled (which criteria were to be considered as important was to be defined and documented at the clean file meeting, prior to code breaking).
2.   An assessment of the primary efficacy variable, ADAS-cog, at 9 months and baseline.
3.   Complied with the trial medication (i.e., have taken at least 75% of the anticipated amount of each component of the IMP).
4.   No other major protocol deviations during the period up to 9 months.
In analyses performed on the PPAS, patients have been analysed as treated.

Subject analysis set title	Follow up analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The FUAS is a subset of the FAS and consists of patients who were eligible and consented to participate in the follow-up part of the trial (6 and 12 months' follow-up [Visits 9 and 10]) and have attended at least 1 of the Follow-up Visits at 6 and 12 months. Patients have been analysed as randomised.

Reporting group values	Safety analysis set	Full analysis set	Per protocol analysis set
Number of subjects	69	62	35
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)	6	6	4
From 65-84 years	61	54	30
85 years and over	2	2	1

Age continuous			
Units: years			
arithmetic mean	72.7	72.6	71.8
standard deviation	± 5.6	± 5.8	± 5.7
Gender categorical			
Units: Subjects			
Female	34	28	16
Male	35	34	19
Ethnic origin			
Units: Subjects			
Caucasian	69	62	35
African descent	0	0	0
Asian or Pacific Islander	0	0	0
Mixed / Multi-racial	0	0	0
Other	0	0	0
Any medical/Surgical history			
Units: Subjects			
Medical/Surgical history reported	39		
No medical/Surgical history reported	30		
Any concurrent disease			
Units: Subjects			
Concurrent disease reported	69		
No concurrent disease reported	0		

Reporting group values	Follow up analysis set		
Number of subjects	41		
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)	4		
From 65-84 years	36		
85 years and over	1		
Age continuous			
Units: years			
arithmetic mean	71.8		
standard deviation	± 5.4		
Gender categorical			
Units: Subjects			
Female	19		
Male	22		
Ethnic origin			
Units: Subjects			
Caucasian	41		
African descent	0		

Asian or Pacific Islander	0		
Mixed / Multi-racial	0		
Other	0		
Any medical/Surgical history Units: Subjects			
Medical/Surgical history reported			
No medical/Surgical history reported			
Any concurrent disease Units: Subjects			
Concurrent disease reported			
No concurrent disease reported			

End points

End points reporting groups

Reporting group title	Apovir
Reporting group description:	

Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant.
Patients randomised to Apovir before first administration of IMP.

Reporting group title	Placebo
Reporting group description:	

Patients were randomised 1:1 to receive Apovir or Placebo. Patients were to be stratified based on presence/absence of treatment with AChEI/Memantine at baseline. However, all patients received treatment with AChEI/Memantine and stratification was therefore not relevant.
Patients randomised to placebo before first administration of IMP.

Reporting group title	Apovir
Reporting group description:	

Patients randomised to Apovir, a combination of APO-P001 and ribavirin. Apovir was taken orally, together with food twice Daily for 9 months. A daily dose of 600 mg APO-P001 and 600 mg ribavirin (decreased to 400 mg for all patients during the trial) were administered by the patients at home.

Reporting group title	Placebo
Reporting group description:	

Patints randomised to placebo. Placebo capsules for APO-P001 and ribavirin respectively were administered twice Daily for 9 months in the same manner as the Apovir capsules.

Reporting group title	Apovir
Reporting group description:	

Patients randomised to Apovir. Follow-up period assessing effect of treatment 6 and 12 months after end of treatment in the Apovir treatment Group.

Reporting group title	Placebo
Reporting group description:	

Patients randomised to Placebo. Follow-up period assessing effect of treatment 6 and 12 months after end of treatment in the Placebo treatment Group.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	

The safety analysis set was defined as all patients who received at least one dose of the IMP. Patients were analysed as treated.

Subject analysis set title	Full analysis set
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	

The FAS is defined as all randomised patients who received at least 1 dose of the IMP and have at least 1 post-baseline assessment of efficacy data. In analyses performed on the FAS, patients have been analysed as randomised.

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	

The PPAS is a subset of the FAS fulfilling the following additional criteria:
1.   All important inclusion criteria and none of the important exclusion criteria were fulfilled (which criteria were to be considered as important was to be defined and documented at the clean file meeting, prior to code breaking).
2.   An assessment of the primary efficacy variable, ADAS-cog, at 9 months and baseline.
3.   Complied with the trial medication (i.e., have taken at least 75% of the anticipated amount of each component of the IMP).
4.   No other major protocol deviations during the period up to 9 months.
In analyses performed on the PPAS, patients have been analysed as treated.

Subject analysis set title	Follow up analysis set

Subject analysis set type	Sub-group analysis

Subject analysis set description:

The FUAS is a subset of the FAS and consists of patients who were eligible and consented to participate in the follow-up part of the trial (6 and 12 months' follow-up [Visits 9 and 10]) and have attended at least 1 of the Follow-up Visits at 6 and 12 months. Patients have been analysed as randomised.

Primary: Change from baseline to 9 months in ADAS-cog total score

End point title	Change from baseline to 9 months in ADAS-cog total score

End point description:

The ADAS-cog test consists of 11 tasks performed by the patient under supervision and measures the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of Alzheimer's disease. The maximum total score is 70. An increase in score indicates a worsening of disease wheras a decrease indicates an improvement.

Sensitivity analyses were performed and are reported as separate endpoints.

End point type	Primary

End point timeframe:

Change from baseline to 9 months

End point values	Apovir	Placebo	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	18	31	49	
Units: ADAS-cog total score				
arithmetic mean (standard deviation)	-1.963 (± 4.398)	1.817 (± 8.623)	0.429 (± 7.531)	

Statistical analyses

Statistical analysis title	Change from baseline to 9 months in ADAS-cog

Statistical analysis description:

The primary efficacy endpoint is the ADAS-cog score at 9 months post baseline. In order to compensate for different baseline ADAS-cog scores, the change from baseline until 9 months post baseline has been used as the primary variable. No imputations of missing data have been done. The hypothesis that the change in ADAS-cog is equal among patients randomised to placebo and patients randomised to Apovir has been tested by means of the exact Wilcoxon rank sum test. The 2-sided p-value is presented

Comparison groups	Apovir v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1809 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The corresponding analysis was done at 3 months p=0.7110, 6 months p=0.1120 and 1 month follow-up p=0.0545

Statistical analysis title	Sensitivity analysis- imputation of data with LOCF

Statistical analysis description:

Sensitivity analyses were performed for the primary efficacy endpoint. The difference between treatment Groups in change from baseline to 9 months in ADAS-cog total score was tested using the Wilcoxon rank sum test imputing missing observations by means of Last Observation Carried Forward (LOCF) princíple.

Comparison groups	Apovir v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.7556
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Sensitivity analysi-imputation of missing data was done with LOCF.
Analysis based on data from the 62 patients in the FAS.

Statistical analysis title	Sensitivity analysis- responder analysis ADAS-cog

Statistical analysis description:

Sensitivity analyses were performed for the primary efficacy endpoint. A responder was defined as having a decrease in ADAS-cog score of at least 4 Points from baseline to 9 months. 3 responder definition criteria were defined for handling of missing data:
1: as non-responders
2: as responders
3: as non-responders in the Apovir Group and as responders in the placebo group

Comparison groups	Apovir v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 1 [4]
Method	Fisher exact

Notes:

[3] - A responder analysis without imputed data had not been pre-specified and is therefore not reported.

Analysis based on data from the 62 patients in the FAS.
[4] - Responder definition 1 p=1.0000
Responder definition 2 p= 0.0092
Responder definition 3 p=0.7707

Statistical analysis title	Sensitivity analysis- responder analysis mean

Statistical analysis description:

Sensitivity analysis were performed for the primary efficacy endpoint. A responder was defined as having a mean decrease in ADAS-cog score of at least 4 Points from baseline across visits at 6 and 9 months and 1 month follow-up. 3 responder definition criteria were defined for handling of missing data:
1: as non-responders
2: as responders
3: as non-responders in the Apovir Group and as responders in the placebo group

Comparison groups	Placebo v Apovir
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.1672 [6]
Method	Fisher exact

Notes:

[5] - Analysis based on data from the 62 patients in the FAS.

[6] - Responder definition 1 p= 0.1672
Responder definition 2 p= 0.0028
Responder definition 3 p= 0.5216

Secondary: Change in ADAS-cog total score - PPAS

End point title	Change in ADAS-cog total score - PPAS

End point description:

The ADAS-cog test consists of 11 tasks performed by the patient under supervision and measures the disturbances of memory, language, praxis, attention and other cognitive abilities which are often

referred to as the core symptoms of Alzheimer's disease. The maximum total score is 70. An increase in score indicates a worsening of disease wheras a decrease indicates an improvement.

End point type	Secondary
End point timeframe:	
From baseline to 9 months	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	25		
Units: ADAS-cog total score				
arithmetic mean (standard deviation)	-2.8 (± 3.94)	0.094 (± 4.836)		

Statistical analyses

Statistical analysis title	Change from baseline to 9 months in ADAS-cog
Comparison groups	Apovir v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1197 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Corresponding analyses were done for 3 months p=0.4545, 6 months p=0.0579 and 1 month follow-up p=0.2019

Secondary: Change from baseline in MMSE score 9 months

End point title	Change from baseline in MMSE score 9 months

End point description:

MMSE is used to test for complaints of memory problems, and to diagnose progresion and severity of dementia. It consists of 30 questions and simple tasks in 6 categories: orientation, registration, attention/calculation, recall, language and coping and gives a maximum total score of 30. A decrease in score indicates a worsening and an increased score indicates an improvement of the condition. The test was performed by the patient under supervision of a physician.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary
End point timeframe:	
Change from baseline to 9 months	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	31		
Units: MMSE score				
arithmetic mean (standard deviation)				
MMSE score	-1.7 (± 2.4)	-1.3 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change fom baseline in MMSE score 6 months

End point title	Change fom baseline in MMSE score 6 months

End point description:

MMSE is used to test for complaints of memory problems, and to diagnose progresion and severity of dementia. It consists of 30 questions and simple tasks in 6 categories: orientation, registration, attention/calculation, recall, language and coping and gives a maximum total score of 30. A decrease in score indicates a worsening and an increased score indicates an improvement of the condition. The test was performed by the patient under supervision of a physician.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Change from baseline to 6 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	30		
Units: MMSE score				
arithmetic mean (standard deviation)				
MMSE score	-1.1 (± 2.5)	-0.8 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in MMSE score 1 month FU

End point title	Change from baseline in MMSE score 1 month FU

End point description:

MMSE is used to test for complaints of memory problems, and to diagnose progresion and severity of dementia. It consists of 30 questions and simple tasks in 6 categories: orientation, registration, attention/calculation, recall, language and coping and gives a maximum total score of 30. A decrease in score indicates a worsening and an increased score indicates an improvement of the condition. The test was performed by the patient under supervision of a physician.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Change from baseline to 1 month after end of treatment

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	30		
Units: MMSE score				
arithmetic mean (standard deviation)				
MMSE score	-0.2 (± 2.3)	-1.7 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDR-SB - 9 months

End point title	Change in CDR-SB - 9 months

End point description:

The CDR consistis of 6 items (boxes) and is a global scale developed to clinically denote the presence of dementia of Alzheimer type and stage its severity. The test was performed by an investigator, nurse or psychologist. Each item was rated 0 to 3 with the score 3 indicating the severest stage. The sum of boxes (CDR-SB) was calculated as the sum of the 6 individual items (0-18).

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Change from baseline to 9 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	28		
Units: CDR-SB				
arithmetic mean (standard deviation)	0.5 (± 1.98)	1.36 (± 2.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ADAS-cog total score - 3 months

End point title	Change in ADAS-cog total score - 3 months

End point description:

The ADAS-cog test consists of 11 tasks performed by the patient under supervision and measures the

disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of Alzheimer's disease. The maximum total score is 70. An increase in score indicates a worsening of disease wheras a decrease indicates an improvement.

End point type	Secondary

End point timeframe:

Change from baseline to 3 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	32		
Units: ADAS-cog total score				
arithmetic mean (standard deviation)	0.475 (± 8.206)	-0.094 (± 5.577)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ADAS-cog total score - 6 months

End point title	Change in ADAS-cog total score - 6 months

End point description:

The ADAS-cog test consists of 11 tasks performed by the patient under supervision and measures the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of Alzheimer's disease. The maximum total score is 70. An increase in score indicates a worsening of disease wheras a decrease indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: ADAS-cog total score				
arithmetic mean (standard deviation)	-1.81 (± 5.403)	0.43 (± 5.798)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ADAS-cog total score - 1 month FU

End point title	Change in ADAS-cog total score - 1 month FU

End point description:

The ADAS-cog test consists of 11 tasks performed by the patient under supervision and measures the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of Alzheimer's disease. The maximum total score is 70. An increase in score indicates a worsening of disease wheras a decrease indicates an improvement.

End point type	Secondary

End point timeframe:

Baseline to 1 month follow-up

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	30		
Units: ADAS-cog total score				
arithmetic mean (standard deviation)	-2.876 (± 3.551)	1.012 (± 8.291)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in CDR-SB - 1 month FU

End point title	Change in CDR-SB - 1 month FU

End point description:

The CDR consistis of 6 items (boxes) and is a global scale developed to clinically denote the presence of dementia of Alzheimer type and stage its severity. The test was performed by an investigator, nurse or psychologist. Each item was rated 0 to 3 with the score 3 indicating the severest stage. The sum of boxes (CDR-SB) was calculated as the sum of the 6 individual items (0-18).

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline to 1 month follow-up

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	29		
Units: CDR-SB				
arithmetic mean (standard deviation)	0.5 (± 2.03)	1.24 (± 3.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AQT color and form -3 months

End point title	Change in AQT color and form -3 months

End point description:

Alzheimer Quick Test (AQT) is a timed test where patients are asked to name 1) color, 2) form and 3) color + form for a series of figures. The total naming time in seconds are recorded. Change from baseline in time for completing the test is presented.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline to 3 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	32		
Units: AQT color and form naming				
arithmetic mean (standard error)	12.2 (± 47.8)	0.9 (± 26.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AQT color and form - 6 months

End point title	Change in AQT color and form - 6 months

End point description:

Alzheimer Quick Test (AQT) is a timed test where patients are asked to name 1) color, 2) form and 3) color + form for a series of figures. The total naming time in seconds are recorded. Change from baseline in time for completing the test is presented.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline to 6 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: AQT color and form naming				
arithmetic mean (standard deviation)	8.6 (± 41.8)	6.8 (± 32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AQT color and form - 9 months

End point title	Change in AQT color and form - 9 months

End point description:

Alzheimer Quick Test (AQT) is a timed test where patients are asked to name 1) color, 2) form and 3) color + form for a series of figures. The total naming time in seconds are recorded. Change from baseline in time for completing the test is presented.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline to 9 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	31		
Units: AQT color and form naming				
arithmetic mean (standard deviation)	-3.9 (± 28.2)	4.8 (± 34.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AQT color and form -1 month FU

End point title	Change in AQT color and form -1 month FU

End point description:

Alzheimer Quick Test (AQT) is a timed test where patients are asked to name 1) color, 2) form and 3) color + form for a series of figures. The total naming time in seconds are recorded. Change from baseline in time for completing the test is presented.

No statistical analysis has been specified for this secondary endpoint.

End point type	Secondary

End point timeframe:

Baseline to 1 month follow-up

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	30		
Units: AQT color and form naming				
arithmetic mean (standard deviation)	-1.9 (± 38.1)	1.7 (± 29.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration APO-P001 - 1 month

End point title	Plasma concentration APO-P001 - 1 month
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
1 month	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: APO-P001 ng/ml				
arithmetic mean (full range (min-max))	1362.9 (684 to 2730)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration APO-P001 - 3 months

End point title	Plasma concentration APO-P001 - 3 months
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: APO-P001 ng/mL				
arithmetic mean (full range (min-max))	1916.3 (792 to 3170)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration APO-P001 - 6 months

End point title	Plasma concentration APO-P001 - 6 months
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
6 months	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: APO-P001 ng/mL				
arithmetic mean (full range (min-max))	2284.8 (1320 to 4830)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration APO-P001 - 9 months

End point title	Plasma concentration APO-P001 - 9 months
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
9 months	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: APO-P001 ng/mL				
arithmetic mean (full range (min-max))	2315.6 (1120 to 4310)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration Ribavirin - 1 month

End point title	Plasma concentration Ribavirin - 1 month
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
1 month	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Ribavirin micromol/L				
arithmetic mean (full range (min-max))	6.56 (2.4 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration Ribavirin - 3 months

End point title	Plasma concentration Ribavirin - 3 months
End point description:	
Plasma samples collected before first IMP dose for the day of sampling.	
End point type	Secondary
End point timeframe:	
3 months	

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Ribavirin micromol/L				
arithmetic mean (full range (min-max))	6.84 (2.8 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration Ribavirin - 6 months

End point title	Plasma concentration Ribavirin - 6 months

End point description:

Plasma samples collected before first IMP dose for the day of sampling.

End point type	Secondary

End point timeframe:

6 months

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Ribavirin micromol/L				
arithmetic mean (full range (min-max))	6.2 (0.3 to 16.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration Ribavirin - 9 months

End point title	Plasma concentration Ribavirin - 9 months

End point description:

Plasma samples collected before first IMP dose for the day of sampling.

End point type	Secondary

End point timeframe:

9 months

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Ribavirin micromol/L				
arithmetic mean (full range (min-max))	5.27 (0.3 to 14.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: CSF concentration APO-P001

End point title	CSF concentration APO-P001

End point description:

CSF samples were collected before first IMP dose for the day of sampling.

End point type	Secondary

End point timeframe:

9 months

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: APO-P001 ng/mL				
arithmetic mean (full range (min-max))	6.576 (2.7 to 17.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: CSF concentration Ribavirin

End point title	CSF concentration Ribavirin

End point description:

CSF samples were collected before first IMP dose for the day of sampling.

End point type	Secondary

End point timeframe:

9 months

End point values	Apovir			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Ribavirin micromol/L				
arithmetic mean (full range (min-max))	3.605 (0.41 to 6.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responder and clinically relevant worsening in ADAS-cog- 9 months

End point title	Responder and clinically relevant worsening in ADAS-cog- 9 months

End point description:

A responder was defined as having a decrease of at least 4 Points compared to baseline. A patient who had an increase in ADAS-cog of at least 4 Points compared to baseline was considered to have a worsening of symptoms.

End point type	Secondary

End point timeframe:

From baseline to 9 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	31		
Units: At least 4 point change in ADAS-cog				
Responder	6	6		
Clinically relevant worsening	1	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder and clinically relevant worsening in ADAS-cog - 3 months

End point title	Responder and clinically relevant worsening in ADAS-cog - 3 months

End point description:

A responder was defined as having a decrease of at least 4 Points compared to baseline. A patient who had an increase in ADAS-cog of at least 4 Points compared to baseline was considered to have a worsening of symptoms.

End point type	Secondary

End point timeframe:

Baseline to 3 months

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	32		
Units: At least 4 point change in ADAS-cog				
Responder	7	6		
Clinically relevant worsening	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder and clinically relevant worsening in ADAS-cog - 6 months

End point title	Responder and clinically relevant worsening in ADAS-cog - 6 months

End point description:

A responder was defined as having a decrease of at least 4 Points compared to baseline. A patient who had an increase in ADAS-cog of at least 4 Points compared to baseline was considered to have a clinically relevant worsening of symptoms.

End point type	Secondary
End point timeframe:	
Baseline to 6 months	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31		
Units: At leats 4 point change in ADAS-cog				
Responder	8	5		
Clinically relevant worsening	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Responder and clinically relevant worsening in ADAS-cog - 1 month FU

End point title	Responder and clinically relevant worsening in ADAS-cog - 1 month FU

End point description:

A responder was defined as having a decrease of at least 4 Points compared to baseline. A patient who had an increase in ADAS-cog of at least 4 Points compared to baseline was considered to have a clinically relevant worsening of symptoms.

End point type	Secondary
End point timeframe:	
Baseline to 1 month follow-up	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	30		
Units: At least 4 point change in ADAS-cog				
Responder	8	6		
Clinically relevant worsening	1	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of Apovir (APO-P001 and Ribavirin)

End point title	Tolerability of Apovir (APO-P001 and Ribavirin)
End point description:	
Tolerability was assessed as the number of patients discontinuing both APO-P001/placebo and Ribavirin/placebo during the treatment period of the trial.	
End point type	Secondary
End point timeframe:	
Treatment period	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Patients				
Dose disconinuation	17	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability APO-P001

End point title	Tolerability APO-P001
End point description:	
Tolerability was assessed as the number of patients with any tolerability issue with APO-P001, dose interruption initiated by patient, dose interuption initiated by Investigator and discontinuation of treatment with APO-P001.	
End point type	Secondary
End point timeframe:	
Treatment period	

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Patients				
Any tolerability	19	3		
Dose interruption initiated by patient	5	2		
Dose interruption initiated by Investigator	1	1		
Dose discontinuation	17	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability Ribavirin

End point title	Tolerability Ribavirin

End point description:

Tolerability was assessed as the number of patients with any tolerability issue with Ribavirin, dose interruption initiated by patient, dose interuption initiated by Investigator and discontinuation of treatment with Ribavirin and Ribavirin dose adjustment.

End point type	Secondary

End point timeframe:

Treatment period

End point values	Apovir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Patients				
Any tolerability	24	5		
Dose interruption initiated by patient	4	1		
Dose interruption initiated by Investigator	0	0		
Dose discontinuation	20	4		
Dose adjustment	9	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The safety reporting period started at administration of the first dose of IMP and ended at the 1 month after end of treatment, ie visit 8.

Adverse event reporting additional description:

Safety was assessed at all visits during the safety reporting period of the trial. A DMC reviewed unblinded safety data continuously during the safety reporting period of the trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1E

Reporting groups

Reporting group title	Apovir

Reporting group description:

Patients randomised to the Apovir Group received Apovir, a combination of APO-P001 and ribavirin, twice Daily for a period of 9 months. Apovir was administered orally and was to be taken together with food.

Reporting group title	Placebo

Reporting group description:

Patients randomised to the Placebo Group received Placebo capsules corresponding to the Apovir capsules. Placebo treatment was administered twice Daily for a period of 9 months as for Apovir. Placebo capsules were administered orally and was to be taken together with food.

Serious adverse events	Apovir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 35 (22.86%)	3 / 34 (8.82%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (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			
Depressed level of consciousness			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Medical device complication			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Gastrointestinal disorders

Abdominal discomfort

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Renal and urinary disorders

Haematuria

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders

Musculoskeletal pain

subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Infections and infestations

Pneumonia

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Urinary tract infection

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 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	Apovir	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 35 (97.14%)	32 / 34 (94.12%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Melanocytic naevus			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 35 (5.71%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 35 (34.29%)	6 / 34 (17.65%)	
occurrences (all)	13	7	
Back pain			
subjects affected / exposed	4 / 35 (11.43%)	3 / 34 (8.82%)	
occurrences (all)	4	3	
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Discomfort			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 35 (5.71%)	1 / 34 (2.94%)	
occurrences (all)	2	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 35 (2.86%)	2 / 34 (5.88%)	
occurrences (all)	1	2	
Investigations			
Weight decreased			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 35 (22.86%)	1 / 34 (2.94%)	
occurrences (all)	8	1	
Amylase increased			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 35 (8.57%)	3 / 34 (8.82%)	
occurrences (all)	3	3	

Fibrin D dimer increased
alternative assessment type: Systematic

subjects affected / exposed	3 / 35 (8.57%)	1 / 34 (2.94%)	
occurrences (all)	3	1	

C-reactive protein increased
alternative assessment type: Systematic

subjects affected / exposed	1 / 35 (2.86%)	2 / 34 (5.88%)	
occurrences (all)	1	2	

Blood creatine increased
alternative assessment type: Systematic

subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	

Injury, poisoning and procedural complications
Fall

subjects affected / exposed	1 / 35 (2.86%)	5 / 34 (14.71%)	
occurrences (all)	1	5	

Nervous system disorders
Headache

subjects affected / exposed	7 / 35 (20.00%)	9 / 34 (26.47%)	
occurrences (all)	11	11	

Syncope

subjects affected / exposed	4 / 35 (11.43%)	1 / 34 (2.94%)	
occurrences (all)	6	1	

Blood and lymphatic system disorders
Haemoglobin decreased
alternative assessment type: Systematic

subjects affected / exposed	16 / 35 (45.71%)	2 / 34 (5.88%)	
occurrences (all)	16	2	

Ear and labyrinth disorders
Vertigo

subjects affected / exposed	1 / 35 (2.86%)	3 / 34 (8.82%)	
occurrences (all)	2	3	

Gastrointestinal disorders

Diarrhoea			
subjects affected / exposed	9 / 35 (25.71%)	4 / 34 (11.76%)	
occurrences (all)	11	7	
Vomiting			
subjects affected / exposed	5 / 35 (14.29%)	4 / 34 (11.76%)	
occurrences (all)	7	4	
Nausea			
subjects affected / exposed	6 / 35 (17.14%)	3 / 34 (8.82%)	
occurrences (all)	6	4	
Abdominal pain upper			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 35 (11.43%)	1 / 34 (2.94%)	
occurrences (all)	4	1	
Hyperhidrosis			
subjects affected / exposed	3 / 35 (8.57%)	0 / 34 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 35 (0.00%)	3 / 34 (8.82%)	
occurrences (all)	0	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 34 (5.88%)	
occurrences (all)	3	3	
Influenza			
subjects affected / exposed	0 / 35 (0.00%)	2 / 34 (5.88%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	The estimated number of patients to be screened was changed from 80 to 120. A possibility for re-screen patients with based on MMSE was introduced for patients with an MMSE score 1-2 Points outisde the acceptable range for inclusion was added to the protocol and a possibility to perform home visits was described.
28 July 2014	The MMSE inclusion criterion was changed from 21-26 to 21-27. The reason for the change was A general dose reduction for ribavirin from 600 mg/day to 400 mg/day was described. The change had been implemented on 03MAR2014 as it was judged that the change was supported by the writing of the clinical trial protocol. The change was implemented because adverse eventsleading to a compromised tolerability in the trial were judged largely to be related to ribavirin had Cognitive tests added at the 1 month follow-up visit. The reason for the change was that adverse events had been reported during the trial that were suspected to interfere with the performance of the cognitive tests The option to temporarily discontinue treatment with ribavirin and/or APO-P001 was introduced. The authority of the DSMB to withdraw patients from the trial or decrease the initial ribavirin dose was extended to include also to temporary or permanently withdraw the ribavirin/placebo treatment also for other reasons
20 November 2014	A long-term post treatment follow-up part consisting of two visits (6 and 12 months after end of treatment) was added to the trial. The reason for adding the visits was to assess the effect of the treatment A clarification of planned statistical analyses was made

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A large proportion of the patients in the Apovir Group discontinued the trial prematuerly. 48.6% of the patients in the Apovir group completed the original part of the trial (1 month after end of treatment) and 34.2% completed the entire trial.

Notes: