Clinical trial results:
A Phase 2a Randomised, Double-Blind, Placebo-Controlled Repeat Dose Trial of the Activity of MDT-637 in Healthy Subjects Challenged with RSV-A (Memphis 37b)

Summary

EudraCT number	2012-001107-20
Trial protocol	GB
Global end of trial date	09 April 2014

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	06 August 2015
Version creation reason	• Correction of full data set QC'd

Trial information

Trial identification

Sponsor protocol code	MDT-637-CP-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Teva: MCD-CS-001

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products, R&D Inc
Sponsor organisation address	41 Moores Road, Frazer, PA, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, +1 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, +1 215-591-3000, ustevatrials@tevapharm.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	23 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective and endpoint of the study is to evaluate the antiviral effect (as defined by reduction in AUC of viral load) of aerosolized MDT-637, in a manner which mimics the timing of the infection and potential treatment application in infants and children.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6), and any applicable national and local laws and regulations (eg, Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union (EU) Directive 2001/20/EC on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use). Information regarding any investigational study centers participating in this study that could not comply with these standards was documented.
Each investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP, and for collecting, recording, and reporting the data accurately and properly. Agreement of each investigator to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where the study center is located.
Written and/or oral information about the study was provided to all subjects in a language understandable by the subjects. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each subject before any study procedures or assessments were done. It was explained to the subjects that they were free to refuse entry into the study and were free to withdraw from the study at any time without prejudice to future treatment.
Each subject’s willingness to participate was documented in writing in a consent form that was signed by the subject with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2013
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	United Kingdom: 143
Worldwide total number of subjects	143
EEA total number of subjects	143

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)	143
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

144 healthy volunteers were screened, enrolled, entered quarantine and were inoculated. One subject withdrew after inoculation but before treatment for personal reasons. This subject was not included in listings, summary tables, or analyses because subjects had to be both inoculated and treated for inclusion
in any of the analysis populations.

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

Blinding implementation details:

Subjects and investigators remained blinded to the treatment assigned during the study, as did the sponsor's clinical personnel who were blinded until the database was locked for analysis and the treatment assignment revealed. The randomization code list was computer generated according to a randomization specification,
using a permuted block algorithm and including stratification by quarantine. Subjects were randomly assigned to treatment through pre-packing of the study drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	MDT-637 BD

Arm description:

MDT-637 administered twice a day (BD) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800 and 2000 hours. Placebo administered via the same dry-powder aerosol inhaler at 1400 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses (14 active, 7 placebo) dispensed over 7 days.

Arm type	Experimental
Investigational medicinal product name	MDT-637
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MDT-637 was administered in aerosolized form via a proprietary, hand-held
device: an MDT-637 EP1C Inhaler. Subjects breathed through a commercially available
facemask that was attached to the device. Each dose of MDT-637 was 132 mcg (ex-face mask). Study drug
(active or placebo) was administered by passive/tidal inhalation, delivered in approximately
2 minutes and approximately 32 tidal breaths. All doses were administered within the Quarantine Unit.

Arm title	MDT-637 TDS

Arm description:

MDT-637 administered three times a day (TDS) via dry-powder, aerosol inhaler at a dose of approximately 132
mcg with daily administration at 0800, 1400 and 2000 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a
positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Arm type	Experimental
Investigational medicinal product name	MDT-637
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

MDT-637 was administered in aerosolized form via a proprietary, hand-held device: an MDT-637 EP1C Inhaler. Subjects breathed through a commercially available facemask that was attached to the device. Each dose of MDT-637 was 132 mcg (ex-face mask). Study drug (active or placebo) was administered by passive/tidal inhalation, delivered in approximately 2 minutes and approximately 32 tidal breaths. All doses were administered within the Quarantine Unit.

Arm title	Placebo

Arm description:

Inhalation grade lactose administered three times a day via dry-powder, aerosol inhaler at 0800, 1400 and 2000 hours. Placebo Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Arm type	Placebo
Investigational medicinal product name	Inhalation grade lactose
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo was administered in aerosolized form via a proprietary, hand-held device: an MDT-637 EP1C Inhaler. Subjects breathed through a commercially available facemask that was attached to the device. Study drug (active or placebo) was administered by passive/tidal inhalation, delivered in approximately 2 minutes and approximately 32 tidal breaths. All doses were administered within the Quarantine Unit.

Number of subjects in period 1	MDT-637 BD	MDT-637 TDS	Placebo
Started	48	48	47
Completed	48	48	47

Baseline characteristics

Reporting groups	
Reporting group title	MDT-637 BD
Reporting group description:	
MDT-637 administered twice a day (BD) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800 and 2000 hours. Placebo administered via the same dry-powder aerosol inhaler at 1400 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses (14 active, 7 placebo) dispensed over 7 days.	
Reporting group title	MDT-637 TDS
Reporting group description:	
MDT-637 administered three times a day (TDS) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800, 1400 and 2000 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.	
Reporting group title	Placebo
Reporting group description:	
Inhalation grade lactose administered three times a day via dry-powder, aerosol inhaler at 0800, 1400 and 2000 hours. Placebo Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.	

Reporting group values	MDT-637 BD	MDT-637 TDS	Placebo
Number of subjects	48	48	47
Age categorical Units: Subjects			
Ages 18 - 44	48	48	47
Age continuous Units: years			
arithmetic mean	24	25.5	24.5
standard deviation	± 4.62	± 5.8	± 5.47
Gender categorical Units: Subjects			
Female	17	13	11
Male	31	35	36
Ethnicity Units: Subjects			
White	39	46	42
Black or African American	3	1	2
Asian	4	1	1
Other or mixed	2	0	2
Nasal wash procedure tolerated at pre-challenge baseline Units: Subjects			
Yes	48	48	46
No	0	0	1
History of smoking Units: Subjects			
Never smoked	29	28	21

Previous smoker	14	8	9
Current smoker	5	12	17
Alcohol use history Units: Subjects			
Never	3	3	4
Previous user	1	1	1
Current user	44	44	42
Any known allergies? Units: Subjects			
Yes	12	8	10
Not recorded	1	1	0
No	35	39	37
Height Units: cm			
arithmetic mean	174.75	175.64	178.43
standard deviation	± 8.046	± 8.922	± 8.658
Weight Units: kg			
arithmetic mean	71.77	72.01	75.41
standard deviation	± 10.05	± 9.471	± 11.87
Body mass index (BMI) Units: kg/m^2			
arithmetic mean	23.5	23.3	23.6
standard deviation	± 2.55	± 2.14	± 2.76

Reporting group values	Total		
Number of subjects	143		
Age categorical Units: Subjects			
Ages 18 - 44	143		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	41		
Male	102		
Ethnicity Units: Subjects			
White	127		
Black or African American	6		
Asian	6		
Other or mixed	4		
Nasal wash procedure tolerated at pre-challenge baseline Units: Subjects			
Yes	142		
No	1		
History of smoking Units: Subjects			

Never smoked	78		
Previous smoker	31		
Current smoker	34		
Alcohol use history Units: Subjects			
Never	10		
Previous user	3		
Current user	130		
Any known allergies? Units: Subjects			
Yes	30		
Not recorded	2		
No	111		
Height Units: cm arithmetic mean standard deviation	- -		
Weight Units: kg arithmetic mean standard deviation	- -		
Body mass index (BMI) Units: kg/m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	MDT-637 BD

Reporting group description:

MDT-637 administered twice a day (BD) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800 and 2000 hours. Placebo administered via the same dry-powder aerosol inhaler at 1400 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses (14 active, 7 placebo) dispensed over 7 days.

Reporting group title	MDT-637 TDS

Reporting group description:

MDT-637 administered three times a day (TDS) via dry-powder, aerosol inhaler at a dose of approximately 132
mcg with daily administration at 0800, 1400 and 2000 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a
positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Reporting group title	Placebo

Reporting group description:

Inhalation grade lactose administered three times a day via dry-powder, aerosol inhaler at 0800, 1400 and 2000 hours. Placebo Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Subject analysis set title	ITT-I MDT-637 BD
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who were randomized to the MDT-637 BD treatment arm and met the criteria for the Intent-to-Treat Infected (ITT-I) population. The Intent-to-Treat Infected population by non-quantitative polymerase chain reaction (non-qPCR) method (ITT-I) was defined as all randomized subjects who received study drug, received challenge virus RSV-A, and provided at least one post-baseline positive non-qPCR result through day 5 post challenge virus administration. It was the primary population for efficacy analysis.

Subject analysis set title	ITT-I MDT-637 TDS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who were randomized to the MDT-637 TDS treatment arm and met the criteria for the Intent-to-Treat Infected (ITT-I) population. The Intent-to-Treat Infected population by non-quantitative polymerase chain reaction (non-qPCR) method (ITT-I) was defined as all randomized subjects who received study drug, received challenge virus RSV-A, and provided at least one post-baseline positive non-qPCR result through day 5 post challenge virus administration. It was the primary population for efficacy analysis.

Subject analysis set title	ITT-I Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who were randomized to the Placebo treatment arm and met the criteria for the Intent-to-Treat Infected (ITT-I) population. The Intent-to-Treat Infected population by non-quantitative polymerase chain reaction (non-qPCR) method (ITT-I) was defined as all randomized subjects who received study drug, received challenge virus RSV-A, and provided at least one post-baseline positive non-qPCR result through day 5 post challenge virus administration. It was the primary population for efficacy analysis.

Subject analysis set title	PK MDT-637 BD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic population consisted of all ITT-I or ITT-I-qPCR subjects who had sufficient data to calculate the pharmacokinetic parameters.

Subject analysis set title	PK MDT-637 TDS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic population consisted of all ITT-I or ITT-I-qPCR subjects who had sufficient data to calculate the pharmacokinetic parameters.

Subject analysis set title	PK Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The pharmacokinetic population consisted of all ITT-I or ITT-I-qPCR subjects who had sufficient data to calculate the pharmacokinetic parameters.

Primary: Area Under the Curve of Viral Load from Day 2 to Day 12 Post Challenge

End point title	Area Under the Curve of Viral Load from Day 2 to Day 12 Post Challenge

End point description:

Subjects were challenged with RSV-A inoculum on day 0. Viral load was measured by non-quantitative polymerase chain reaction (non-qPCR) on nasal wash which was performed twice daily. AUC of viral load was calculated by a linear trapezoidal summation method using actual sampling times in the calculations.
PFU = plaque-forming units.

End point type	Primary

End point timeframe:

Day 2 to the last day of discharge from quarantine (usually Day 12)

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: Log10 PFU/mL-days				
arithmetic mean (confidence interval 95%)	33.95 (29.718 to 38.182)	30.62 (25.161 to 36.079)	29.175 (24.299 to 34.051)	

Statistical analyses

Statistical analysis title	AUC of Viral Load: MDT-637 TDS to Placebo

Statistical analysis description:

Since there were 3 pairwise comparisons for the primary endpoint, a fixed-sequence testing procedure was used in the following order:
1. MDT-637 TDS vs. placebo
2. MDT-637 BD vs. placebo
3. MDT-637 TDS vs. MDT-637 BD

Comparison groups	ITT-I Placebo v ITT-I MDT-637 TDS
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6692 [1]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	1.445

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.25
upper limit	8.141

Notes:

[1] - Single fixed effect of treatment. Comparison was performed at the 0.05 significance level.

Statistical analysis title	AUC of Viral Load: MDT-637 BD to Placebo

Statistical analysis description:

Since there were 3 pairwise comparisons for the primary endpoint, a fixed-sequence testing procedure was used in the following order:
1. MDT-637 TDS vs. placebo
2. MDT-637 BD vs. placebo
3. MDT-637 TDS vs. MDT-637 BD

Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1566 [2]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	4.775
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.865
upper limit	11.416

Notes:

[2] - Single fixed effect of treatment. Comparison was performed at the 0.05 significance level.

Statistical analysis title	AUC of Viral Load: MDT-637 TDA to MDT-637-BD

Statistical analysis description:

Since there were 3 pairwise comparisons for the primary endpoint, a fixed-sequence testing procedure was used in the following order:
1. MDT-637 TDS vs. placebo
2. MDT-637 BD vs. placebo
3. MDT-637 TDS vs. MDT-637 BD

Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3364 [3]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-3.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.172
upper limit	3.512

Notes:

[3] - Single fixed effect of treatment. Comparison was performed at the 0.05 significance level.

Secondary: Duration of Viral Shedding by Tissue Culture

End point title	Duration of Viral Shedding by Tissue Culture

End point description:

Duration of virus shedding was calculated as the number of days elapsed from the date of first detection of RSV-A to the date when virus first became undetectable.

End point type	Secondary

End point timeframe:

Day 1 to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	28	32	
Units: days				
arithmetic mean (standard deviation)	5.4 (± 2.16)	4.8 (± 1.91)	5.5 (± 1.92)	

Statistical analyses

Statistical analysis title	Duration Viral Shedding: MDT-637 TDS to Placebo

Statistical analysis description:

Duration of Viral Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2139 [4]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.4

Notes:

[4] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Duration Viral Shedding: MDT-637 BD to Placebo

Statistical analysis description:

Duration of Viral Shedding by Tissue Culture

Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9682 [5]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[5] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Duration Viral Shedding: MDT-637 TDS - MDT-637-BD

Statistical analysis description:

Duration of Viral Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2396 [6]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.4

Notes:

[6] - Comparison was performed at the 0.05 significance level.

Secondary: Peak Virus Shedding By Tissue Culture

End point title	Peak Virus Shedding By Tissue Culture

End point description:

Peak virus shedding was calculated as maximum viral load assessment.

End point type	Secondary

End point timeframe:

Day 1 to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	28	32	
Units: log10PFU/mL				
arithmetic mean (standard deviation)	4.43 (± 1.4084)	4.58 (± 1.5063)	4.512 (± 1.1619)	

Statistical analyses

Statistical analysis title	Peak Virus Shedding: MDT-637 TDS to Placebo
Statistical analysis description: Peak Virus Shedding By Tissue Culture	
Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8468 [7]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.631
upper limit	0.767

Notes:

[7] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Peak Virus Shedding: MDT-637 BD to Placebo
Statistical analysis description: Peak Virus Shedding By Tissue Culture	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8154 [8]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	-0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.774
upper limit	0.611

Notes:

[8] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Peak Virus Shedding: MDT-637-TDS to MDT-637-BD

Statistical analysis description:	
Peak Virus Shedding By Tissue Culture	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6785 [9]
Method	ANOVA
Parameter estimate	Difference in LSM
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.566
upper limit	0.865

Notes:

[9] - Comparison was performed at the 0.05 significance level.

Secondary: Total Area Under the Curve (AUC) of Virus Shedding by Tissue Culture

End point title	Total Area Under the Curve (AUC) of Virus Shedding by Tissue Culture

End point description:

AUC of virus shedding post challenge, per day (cumulative endpoint) for day X (where X was from day 2 after the viral challenge through to day 12) was calculated based on tissue culture data by linear trapezoidal summation method.

End point type	Secondary

End point timeframe:

Day 2 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: Log10PFU/mL-days				
arithmetic mean (standard deviation)	14.683 (± 8.4465)	14.767 (± 8.8548)	13.831 (± 7.4745)	

Statistical analyses

Statistical analysis title	AUC Viral Shedding: MDT-637 TDS to Placebo

Statistical analysis description:

Total Area Under the Curve (AUC) of Virus Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6466 [10]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	0.936
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.103
upper limit	4.974

Notes:

[10] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	AUC Viral Shedding: MDT-637 BD to Placebo
Statistical analysis description:	
Total Area Under the Curve (AUC) of Virus Shedding by Tissue Culture	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6736 [11]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	0.852
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.152
upper limit	4.857

Notes:

[11] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	AUC Viral Shedding: MDT-637 TDS to MDT-637 BD
Statistical analysis description:	
Total Area Under the Curve (AUC) of Virus Shedding by Tissue Culture	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9681 [12]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.043
upper limit	4.21

Notes:

[12] - Comparison was performed at the 0.05 significance level.

Secondary: Kaplan-Meier Estimates for Time to Peak Shedding by Tissue Culture

End point title	Kaplan-Meier Estimates for Time to Peak Shedding by Tissue Culture

End point description:

Time to peak shedding was calculated as the number of days between time of first detection of RSV-A and time of maximum viral load.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	28	32	
Units: days				
median (confidence interval 95%)	3 (1 to 3)	2 (1 to 2)	2 (2 to 3)	

Statistical analyses

Statistical analysis title	Time to Peak Shedding: MDT-637 TDS to Placebo

Statistical analysis description:

Kaplan-Meier Estimates for Time to Peak Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3619 [13]
Method	Logrank

Notes:

[13] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Peak Shedding: MDT-637 BD to Placebo

Statistical analysis description:

Kaplan-Meier Estimates for Time to Peak Shedding by Tissue Culture

Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7184 [14]
Method	Logrank

Notes:

[14] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Peak Shedding: MDT-637 TDS to MDT-637-BD

Statistical analysis description:

Kaplan-Meier Estimates for Time to Peak Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1851 [15]
Method	Logrank

Notes:

[15] - Comparison was performed at the 0.05 significance level.

Secondary: Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding by Tissue Culture

End point title	Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding by Tissue Culture

End point description:

Time to resolution from peak viral shedding was calculated as number of days between time of maximum viral load and first time when virus became undetectable.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	28	32	
Units: days				
median (confidence interval 95%)	3 (2 to 4)	3 (2 to 3)	3 (2 to 4)	

Statistical analyses

Statistical analysis title	Time to Resolve: MDT-637 TDS to Placebo

Statistical analysis description:

Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding by Tissue Culture

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3896 [16]
Method	Logrank

Notes:

[16] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Resolve: MDT-637 BD to Placebo

Statistical analysis description:	
Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding by Tissue Culture	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7798 [17]
Method	Logrank

Notes:

[17] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Resolve: MDT-637 TDS to MDT-637 BD
Statistical analysis description:	
Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding by Tissue Culture	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5583 [18]
Method	Logrank

Notes:

[18] - Comparison was performed at the 0.05 significance level.

Secondary: Duration of Virus Shedding By Quantitative Polymerase Chain Reaction Assay

End point title	Duration of Virus Shedding By Quantitative Polymerase Chain Reaction Assay
End point description:	
Duration of virus shedding was calculated as the number of days elapsed from the date of first detection of RSV-A to the date when virus first became undetectable.	
End point type	Secondary
End point timeframe:	
Day 1 to day 12	

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	34	
Units: days				
arithmetic mean (standard deviation)	17.69 (± 9.204)	15.4 (± 9.363)	16.63 (± 9.133)	

Statistical analyses

Statistical analysis title	Duration Viral Shedding: MDT-637 TDS to Placebo
Statistical analysis description:	
Duration of Virus Shedding By Quantitative Polymerase Chain Reaction Assay	

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5931 [19]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.78
upper limit	3.32

Notes:

[19] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Duration Viral Shedding: MDT-637 BD to Placebo
Statistical analysis description:	
Duration of Virus Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6436 [20]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	5.57

Notes:

[20] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Duration Viral Shedding: MDT-637 TDS to MDT-637 BD
Statistical analysis description:	
Duration of Virus Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3286 [21]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-2.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	2.33

Notes:

[21] - Comparison was performed at the 0.05 significance level.

Secondary: Peak Virus Shedding By Quantitative Polymerase Chain Reaction Assay

End point title	Peak Virus Shedding By Quantitative Polymerase Chain Reaction Assay

End point description:

Peak virus shedding was calculated as maximum viral load assessment.

End point type	Secondary

End point timeframe:

Day 1 to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	34	
Units: log10PFU/mL				
arithmetic mean (standard deviation)	6.108 (± 1.1872)	5.822 (± 1.7543)	5.952 (± 1.3753)	

Statistical analyses

Statistical analysis title	Peak Viral Shedding: MDT-637 TDS to Placebo

Statistical analysis description:

Peak Virus Shedding By Quantitative Polymerase Chain Reaction Assay

Comparison groups	ITT-I Placebo v ITT-I MDT-637 TDS
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7186 [22]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.847
upper limit	0.586

Notes:

[22] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Peak Viral Shedding: MDT-637 BD to Placebo
Statistical analysis description:	
Peak Virus Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6644 [23]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.555
upper limit	0.866

Notes:

[23] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Peak Viral Shedding: MDT-637 TDS to MDT-637 BD
Statistical analysis description:	
Peak Virus Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4364 [24]
Method	ANOVA
Parameter estimate	Difference of LSM
Point estimate	-0.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.013
upper limit	0.441

Notes:

[24] - Comparison was performed at the 0.05 significance level.

Secondary: Kaplan-Meier Estimates for Time to Peak Shedding By Quantitative Polymerase Chain Reaction Assay

End point title	Kaplan-Meier Estimates for Time to Peak Shedding By Quantitative Polymerase Chain Reaction Assay

End point description:

Time to peak virus shedding from the nasal mucosa was calculated as the number of days between time of first detection of RSV-A and time of maximum viral load.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	34	
Units: days				
median (confidence interval 95%)	4 (3.5 to 4)	3.5 (3 to 4)	4 (3 to 5)	

Statistical analyses

Statistical analysis title	Time to Peak Shedding: MDT-637 TDS to Placebo
Statistical analysis description: Kaplan-Meier Estimates for Time to Peak Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2303 [25]
Method	Logrank

Notes:
[25] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Peak Shedding: MDT-637 BD to Placebo
Statistical analysis description: Kaplan-Meier Estimates for Time to Peak Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7188 [26]
Method	Logrank

Notes:
[26] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Peak Shedding: MDT-637 TDS to MDT-637-BD
Statistical analysis description: Kaplan-Meier Estimates for Time to Peak Shedding By Quantitative Polymerase Chain Reaction Assay	
Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4078 [27]
Method	Logrank

Notes:

[27] - Comparison was performed at the 0.05 significance level.

Secondary: Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding By Quantitative Polymerase Chain Reaction Assay

End point title	Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding By Quantitative Polymerase Chain Reaction Assay

End point description:

Time to resolution from peak viral shedding was calculated as the number of days between time of maximum viral load and first time when virus became undetectable.

End point type	Secondary

End point timeframe:

Day 1 to day 28

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	34	
Units: days				
median (confidence interval 95%)	14.75 (6.5 to 19)	7 (4.5 to 17.5)	7.25 (5.5 to 19)	

Statistical analyses

Statistical analysis title	Time to Resolve: MDT-637 TDS to Placebo

Statistical analysis description:

Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding By Quantitative Polymerase Chain Reaction Assay

Comparison groups	ITT-I MDT-637 TDS v ITT-I Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9607 [28]
Method	Logrank

Notes:

[28] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Resolve: MDT-637 BD to Placebo

Statistical analysis description:

Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding By Quantitative Polymerase Chain Reaction Assay

Comparison groups	ITT-I Placebo v ITT-I MDT-637 BD

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3501 [29]
Method	Logrank

Notes:

[29] - Comparison was performed at the 0.05 significance level.

Statistical analysis title	Time to Resolve: MDT-637 TDS to MDT-637 BD

Statistical analysis description:

Kaplan-Meier Estimates for Time to Resolution from Peak Viral Shedding By Quantitative Polymerase Chain Reaction Assay

Comparison groups	ITT-I MDT-637 BD v ITT-I MDT-637 TDS
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3238 [30]
Method	Logrank

Notes:

[30] - Comparison was performed at the 0.05 significance level.

Secondary: Total Mucus Weight by Study Phase

End point title	Total Mucus Weight by Study Phase

End point description:

Subjects were given pre-weighed packets of paper tissues (handkerchiefs). Subjects stored each tissue used for nose blowing or sneezing in an airtight plastic bag. Bags of used tissues were collected daily (24-hour collection) and new bags were distributed. All paper tissues used by each subject were collected for each 24-hour period throughout the quarantine period, to determine the total weight of mucus produced

End point type	Secondary

End point timeframe:

After viral challenge: Day 1 up to day 5
Dosing phase: When PRC positive or Day 5 at latest, to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: grams				
arithmetic mean (standard deviation)				
After viral challenge	29.35 (± 30.173)	26.88 (± 26.451)	30.24 (± 40.929)	
Dosing phase	27.48 (± 29.995)	25.46 (± 25.836)	27.49 (± 39.683)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Tissues Used by Study Phase

End point title	Total Number of Tissues Used by Study Phase

End point description:

Subjects were given pre-weighed packets of paper tissues (handkerchiefs). Subjects stored each tissue used for nose blowing or sneezing in an airtight plastic bag. All paper tissues used by each subject were collected for each 24-hour period throughout the quarantine period, to determine the total weight of mucus produced, and the total number of tissues used.

End point type	Secondary

End point timeframe:

After viral challenge: Day 1 up to day 5
Dosing phase: When PRC positive or Day 5 at latest, to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: number of tissues				
arithmetic mean (standard deviation)				
After viral challenge	58.9 (± 57.65)	65.3 (± 68.35)	54.6 (± 59.4)	
Dosing phase	54.6 (± 56.2)	61.3 (± 66.01)	48.9 (± 57.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Grade 2 or Worse Symptoms At Any Day Post Inoculation

End point title	Percentage of Subjects With Grade 2 or Worse Symptoms At Any Day Post Inoculation

End point description:

Subjects were asked to assess challenge virus-related signs and symptoms, and associated severity at scheduled times throughout the quarantine period, and to record the signs and symptoms in the subject diary card. The symptoms that the subjects were asked to assess were: runny nose, stuffy nose, sneezing, sore throat, earache, malaise (tiredness), cough, shortness of breath, headache, and muscle and/or joint pain. For each symptom, subjects were asked to check
the rating that best described how they felt since completing the last diary card, using the following categories:
Grade 0 indicated no symptoms.
Grade 1 meant symptoms were just noticeable.
Grade 2 symptoms indicated 'It's clearly bothersome from time to time, but it doesn't stop me from participating in activities',
Grade 3 indicated 'It's quite bothersome, most or all of the time, and it stops me from participating in activities'.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: percentage of subjects				
number (not applicable)	71.9	71	74.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Grade 2 or Worse Symptoms

End point title	Duration of Grade 2 or Worse Symptoms

End point description:

The duration of Grade 2 or worse symptoms was calculated as number of days elapsed from the date of first occurrence of any Grade >2 symptom to the date of last occurrence of any Grade >2 symptom as recorded by subjects in the Symptom Diary Cards.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	23[31]	22[32]	26[33]	
Units: days				
arithmetic mean (standard deviation)	3.7 (± 1.99)	5 (± 2.8)	5.5 (± 3.34)	

Notes:

[31] - Subjects with grade 2 or worse clinical symptoms

[32] - Subjects with grade 2 or worse clinical symptoms

[33] - Subjects with grade 2 or worse clinical symptoms

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Grade 1 or Worse Symptoms At Any Day During the Dose Phase

End point title	Percentage of Subjects With Grade 1 or Worse Symptoms At Any Day During the Dose Phase

End point description:

Subjects were asked to assess challenge virus-related signs and symptoms, and associated severity at scheduled times throughout the quarantine period, and to record the signs and symptoms in the subject diary card. Symptoms were: runny nose, stuffy nose, sneezing, sore throat, earache, malaise (tiredness), cough, shortness of breath, headache, and muscle and/or joint pain. Ratings since completing the previous card were:

0="I have NO symptoms";
1="Just noticeable";
2="It's clearly bothersome from time to time, but it doesn't stop me from participating in activities";
3="It's quite bothersome, most or all of the time and it stops me from participating in activities".

End point type	Secondary

End point timeframe:

Dose phase: When PRC positive or Day 5 at latest, to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: percentage of subjects				
number (not applicable)	90.6	96.8	97.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Grade 1 or Worse of Three Symptom Categories (Upper Respiratory Tract, Lower Respiratory Tract, Systemic Symptoms) At Any Day Post Inoculation

End point title	Percentage of Subjects With Grade 1 or Worse of Three Symptom Categories (Upper Respiratory Tract, Lower Respiratory Tract, Systemic Symptoms) At Any Day Post Inoculation

End point description:

The percentage of subjects with Grade ≥1 symptom score was calculated for upper respiratory tract (URTI) symptoms, lower respiratory tract symptoms and systemic symptoms (ie, malaise and muscle and/or joint aches). The numerator for the proportion was the number of subjects who experienced URTI (or other category) symptoms at any time during post inoculation. The denominator was the number of subjects with at least one record in the symptom diary card post inoculation. The proportion was then multiplied by 100 to create the percentage.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: percentage of subjects				
number (not applicable)				
Upper respiratory tract	96.9	96.8	97.1	
Lower respiratory tract	65.6	48.4	54.3	
Systemic symptoms	75	83.9	85.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Peak Symptoms Recorded on the Symptom Diary Card

End point title	Time to Peak Symptoms Recorded on the Symptom Diary Card

End point description:

Time to peak of each reported symptom was calculated as the number of days between administration of virus inoculum and time when the symptom reached its maximum severity. If the duration of maximum was several days, the earliest occurrence was used in the calculations.

End point type	Secondary

End point timeframe:

Day 1 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32[34]	31[35]	35[36]	
Units: days				
median (confidence interval 95%)				
Runny nose (n=24, 24, 24)	6 (5 to 7)	7 (5 to 7)	6 (5 to 6)	
Stuffy nose (n=29, 29, 34)	5 (5 to 6)	6 (5 to 7)	6 (5 to 6)	
Sneezing (n=24, 25, 25)	5 (4 to 6)	6 (6 to 7)	6 (4 to 6)	
Sore throat (n=24, 27, 31)	5 (5 to 6)	5 (4 to 6)	5 (4 to 6)	
Earache (n=8, 7, 10)	6.5 (1 to 9)	5 (2 to 7)	5.5 (4 to 7)	
Cough (n=20, 15, 17)	5 (4 to 7)	6 (4 to 7)	6 (2 to 7)	
Shortness of breath (n=5, 3, 6)	5 (5 to 6)	2 (2 to 6)	6 (4 to 11)	
Malaise (n=19, 18, 20)	5 (3 to 6)	6 (5 to 7)	6 (3 to 7)	
Headache (n=18, 22, 26)	6 (5 to 7)	5.5 (5 to 6)	5.5 (3 to 6)	
Muscle and/or joint ache (n=7, 14, 11)	4 (2 to 5)	4.5 (2 to 6)	4 (1 to 6)	

Notes:

[34] - Population counts for each symptom follow the symptom name.

[35] - Population counts for each symptom follow the symptom name.

[36] - Population counts for each symptom follow the symptom name.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Pyrexia At Any Day Post Inoculation

End point title	Percentage of Subjects with Pyrexia At Any Day Post Inoculation

End point description:

Pyrexia was defined as a temperature of >37.9°C or two SDs greater than the average of the 3 last

non-missing assessments prior to the virus inoculum. A subject was considered to have a febrile illness post-challenge if he/she had any occurrence of a temperature of ≥37.9°C (confirmed by a repeat measurement as ≥37.9°C within 20 to 60 minutes) between day 0 and the last day of receiving study drug.

End point type	Secondary

End point timeframe:

Day 0 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: percentage of subjects				
number (not applicable)	28.1	22.6	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of Pyrexia

End point title	Mean Duration of Pyrexia

End point description:

Mean duration of pyrexia was defined as the number of hours with pyrexia.

End point type	Secondary

End point timeframe:

Day 0 to day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[37]	7[38]	7[39]	
Units: hours				
arithmetic mean (standard deviation)	23.639 (± 19.9069)	24.667 (± 35.1291)	16.324 (± 8.1769)	

Notes:

[37] - Subjects with pyrexia

[38] - Subjects with pyrexia

[39] - Subjects with pyrexia

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve of Temperature During the Dosing Phase

End point title	Area Under the Curve of Temperature During the Dosing Phase

End point description:

The AUC of temperature during the dosing phase included all time points and was calculated by a linear trapezoidal method.

End point type	Secondary

End point timeframe:

Dosing phase: When PRC positive or Day 5 at latest, to Day 12

End point values	ITT-I MDT-637 BD	ITT-I MDT-637 TDS	ITT-I Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	35	
Units: °C*days				
arithmetic mean (standard deviation)	298.6 (± 26.812)	300.18 (± 30.899)	294.16 (± 30.846)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Successful Doses As Observed by Study Staff

End point title	Percentage of Successful Doses As Observed by Study Staff

End point description:

Treatment compliance was calculated as the number of successful doses taken as observed by study staff taken by the planned number of doses and multiplied by 100%.

End point type	Secondary

End point timeframe:

Dosing phase: When PRC positive or Day 5 at latest, to Day 12

End point values	MDT-637 BD	MDT-637 TDS	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[40]	48[41]	47[42]	
Units: percentage of total doses				
number (not applicable)	100	100	100	

Notes:

[40] - Intent to treat population

[41] - Intent to treat population

[42] - Intent to treat population

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Adverse Events

End point title	Summary of Adverse Events

End point description:

An adverse event was defined in the protocol as any untoward medical occurrence in a clinical study subject to which study drug (active or placebo) had been administered, including occurrences that were not necessarily caused by or related to that product.
Treatment-emergent AEs are those that started after the first dose of study drug.
AE severity was rated as mild (mild level of discomfort and did not interfere with regular activities), moderate, severe (significant level of discomfort and prevented regular activities) or life-threatening.
The investigator determined whether there was a reasonable possibility of treatment relation.
A serious adverse event was an adverse event that resulted in any of the following outcomes or actions:
Death
Life threatening
Required inpatient hospitalization/prolongation of hospitalization
Resulted in persistent or significant disability/incapacity
Congenital anomaly/birth defect
An other important medical event

End point type	Secondary

End point timeframe:

Day 0 to day 12

End point values	MDT-637 BD	MDT-637 TDS	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48[43]	48[44]	47[45]	
Units: subjects				
1+ AE	31	32	34	
1+ treatment-emergent AE (TEAE)	25	30	30	
Mild TEAE	22	24	24	
Moderate TEAE	2	5	6	
Severe TEAE	1	1	0	
Related TEAE	6	9	11	
TEAE related to challenge virus	11	8	14	
TEAE related to challenge virus + study drug	4	6	8	
TEAE related to study procedure/assessment	6	5	9	
TEAE related to concomitant med	5	5	8	
TEAE related to device	0	0	0	
Adverse device effect	0	0	0	
Device deficiency	0	0	0	
Serious TEAE	0	0	0	

Notes:

[43] - Safety population

[44] - Safety population

[45] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Drug Concentration (Cmax)

End point title	Maximum Observed Plasma Drug Concentration (Cmax)

End point description:

Blood samples to determine the pharmacokinetic profile of MDT-637 in plasma of subjects inoculated with RSV-A were taken only in the subjects who participated in quarantine 2, and were linked to the

morning dose.

End point type	Secondary

End point timeframe:

Days 6 and 12 (dose days 2 and 7): predose (0 hours -15 minutes), 0.5, 1, 2, 3, 4, 6, 12, 12.5, 13, 14, 16, 18, and 24 hours

End point values	PK MDT-637 BD	PK MDT-637 TDS	PK Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10[46]	9[47]	0[48]	
Units: pg/mL				
arithmetic mean (standard deviation)				
Dose day 2	22.1 (± 5.9)	33.6 (± 10.6)	()	
Dose day 7	25.6 (± 9.4)	34.7 (± 9)	()	

Notes:

[46] - Subjects from quarantine 2 only

[47] - Subjects from quarantine 2 only

[48] - Placebo-treated subjects do not have MDT-637 PK results reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Maximum Observed Drug Concentration (Tmax)

End point title	Time To Maximum Observed Drug Concentration (Tmax)

End point description:

Blood samples to determine the pharmacokinetic profile of MDT-637 in plasma of subjects inoculated with RSV-A were taken only in the subjects who participated in quarantine 2, and were linked to the morning dose.

End point type	Secondary

End point timeframe:

Days 6 and 12 (dose days 2 and 7): predose (0 hours -15 minutes), 0.5, 1, 2, 3, 4, 6, 12, 12.5, 13, 14, 16, 18, and 24 hours

End point values	PK MDT-637 BD	PK MDT-637 TDS	PK Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10[49]	9[50]	0[51]	
Units: hour				
arithmetic mean (standard deviation)				
Dose day 2	15.5 (± 1.7)	13.6 (± 1.1)	()	
Dose day 7	7.7 (± 7.1)	13.4 (± 4.8)	()	

Notes:

[49] - Subjects from quarantine 2 only

[50] - Subjects from quarantine 2 only

[51] - Placebo-treated subjects do not have MDT-637 PK results reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Plasma-Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC0-t)

End point title	Area Under The Plasma-Concentration-Time Curve From Time 0 To The Time Of The Last Measurable Drug Concentration (AUC0-t)

End point description:

Blood samples to determine the pharmacokinetic profile of MDT-637 in plasma of subjects inoculated with RSV-A were taken only in the subjects who participated in quarantine 2, and were linked to the morning dose.

End point type	Secondary

End point timeframe:

Days 6 and 12 (dose days 2 and 7): predose (0 hours -15 minutes), 0.5, 1, 2, 3, 4, 6, 12, 12.5, 13, 14, 16, 18, and 24 hours

End point values	PK MDT-637 BD	PK MDT-637 TDS	PK Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10[52]	9[53]	0[54]	
Units: hour*pg/mL				
arithmetic mean (standard deviation)				
Dose day 2	388 (± 113)	599 (± 190)	()	
Dose day 7	473 (± 207)	614 (± 149)	()	

Notes:

[52] - Subjects from quarantine 2 only

[53] - Subjects from quarantine 2 only

[54] - Placebo-treated subjects do not have MDT-637 PK results reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞)

End point title	Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞)

End point description:

Blood samples to determine the pharmacokinetic profile of MDT-637 in plasma of subjects inoculated with RSV-A were taken only in the subjects who participated in quarantine 2, and were linked to the morning dose.

Results are not reported because different dosing schedules and the same sampling times for the two MDT treatments meant that results for derived pharmacokinetic variables would not be comparable.

End point type	Secondary

End point timeframe:

Days 6 and 12 (dose days 2 and 7): predose (0 hours -15 minutes), 0.5, 1, 2, 3, 4, 6, 12, 12.5, 13, 14, 16, 18, and 24 hours

End point values	PK MDT-637 BD	PK MDT-637 TDS	PK Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[55]	0[56]	0[57]	
Units: h*pg/mL				
arithmetic mean (standard deviation)				
Dose day 2	()	()	()	
Dose day 7	()	()	()	

Notes:

[55] - Different dosing schedules for the two MDT arms meant results for derived PK were not comparable.
[56] - Different dosing schedules for the two MDT arms meant results for derived PK were not comparable.
[57] - Placebo-treated subjects do not have MDT-637 PK results reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half life (t½)

End point title	Elimination half life (t½)

End point description:

Blood samples to determine the pharmacokinetic profile of MDT-637 in plasma of subjects inoculated with RSV-A were taken only in the subjects who participated in quarantine 2, and were linked to the morning dose.
Results are not reported because different dosing schedules and the same sampling times for the two MDT treatments meant that results for derived pharmacokinetic variables would not be comparable.

End point type	Secondary

End point timeframe:

Days 6 and 12 (dose days 2 and 7): predose (0 hours -15 minutes), 0.5, 1, 2, 3, 4, 6, 12, 12.5, 13, 14, 16, 18, and 24 hours

End point values	PK MDT-637 BD	PK MDT-637 TDS	PK Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[58]	0[59]	0[60]	
Units: hour				
arithmetic mean (standard deviation)				
Dose day 2	()	()	()	
Dose day 7	()	()	()	

Notes:

[58] - Different dosing schedules for the two MDT arms meant results for derived PK were not comparable
[59] - Different dosing schedules for the two MDT arms meant results for derived PK were not comparable
[60] - Placebo-treated subjects do not have MDT-637 PK results reported.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Dosing phase: When PRC positive or Day 5 at latest, to Day 12

Adverse event reporting additional description:

The symptoms that were recorded on the diary cards were presumed to represent challenge virus infection consequent to challenge, and were not to be captured as adverse events unless they met one of the criteria for a serious adverse event. However, this was not followed consistently as there were no SAEs but there were TEAEs with those symptoms.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	MDT-637 BD

Reporting group description:

MDT-637 administered twice a day (BD) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800 and 2000 hours. Placebo administered via the same dry-powder aerosol inhaler at 1400 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses (14 active, 7 placebo) dispensed over 7 days.

Reporting group title	MDT-637 TDS

Reporting group description:

MDT-637 administered three times a day (TDS) via dry-powder, aerosol inhaler at a dose of approximately 132 mcg with daily administration at 0800, 1400 and 2000 hours. Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Reporting group title	Placebo

Reporting group description:

Inhalation grade lactose administered three times a day via dry-powder, aerosol inhaler at 0800, 1400 and 2000 hours. Placebo Dosing commenced on Days 2, 3, 4 or 5, post-inoculum dependent on a positive non-qPCR nasal wash result for the presence of the challenge virus. The total dose was up to 21 consecutive doses dispensed over 7 days.

Serious adverse events	MDT-637 BD	MDT-637 TDS	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	MDT-637 BD	MDT-637 TDS	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 48 (33.33%)	12 / 48 (25.00%)	19 / 47 (40.43%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 48 (8.33%)	5 / 48 (10.42%)	5 / 47 (10.64%)
occurrences (all)	4	5	5
Spirometry abnormal			
subjects affected / exposed	2 / 48 (4.17%)	2 / 48 (4.17%)	3 / 47 (6.38%)
occurrences (all)	2	3	3
Forced expiratory volume decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	4 / 47 (8.51%)
occurrences (all)	0	1	5
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	3 / 48 (6.25%)	2 / 48 (4.17%)	2 / 47 (4.26%)
occurrences (all)	3	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 48 (6.25%)	2 / 48 (4.17%)	7 / 47 (14.89%)
occurrences (all)	3	2	7
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 48 (4.17%)	1 / 48 (2.08%)	3 / 47 (6.38%)
occurrences (all)	2	1	5
Cough			
subjects affected / exposed	3 / 48 (6.25%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences (all)	3	0	1
Nasal congestion			
subjects affected / exposed	3 / 48 (6.25%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2013	Amendment 1 (dated 10 July 2013) to the protocol was issued before any subjects were enrolled into the study. The following major procedural changes (not all-inclusive) were made to the protocol: - The following secondary objectives were added: antiviral effect (as defined by reduction in log AUC viral load by TCID50), and performance and safety of the inhaler device. - The inclusion and exclusion criteria were clarified - The study procedures were clarified
11 September 2013	Amendment 2 (dated 11 September 2013) to the protocol was issued after screening had started but before any subjects entered quarantine. The following major procedural changes (not all-inclusive) were made to the protocol: - The BD dosing regimen was added - Further information was added on the background to the product, the use of the facemask and device, risk-benefit assessment, and definitions and reporting requirements of any adverse reactions to the EP1C inhaler device. - The sponsor was changed from MicroDose to Teva, which resulted in a change of pharmacovigilance reporting procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported