Sponsor

Novartis Pharmaceuticals

Generic Drug Name

RSV604

Trial Indication(s)

Respiratory syncytial virus

Protocol Number

CRSV604A2203

Protocol Title

A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and efficacy of oral RSV604 in healthy adults experimentally infected with respiratory syncytial virus

Clinical Trial Phase

Phase IIa

Study Start/End Dates

17-Jun-2008 to 17-Jun-2009

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled study employing an adaptive design. All subjects were inoculated with RSV on Day 0 and given study drug (RSV604 for oral administration) at different times during the infection period, depending on the cohort. Dose administration relative to day of inoculation was as follows:

- Cohort 1: No administration of study drug. The purpose of enrolling this cohort was to study the infection rate.
- Cohort 2: RSV604 administered 48 hr post inoculation with RSV.
- Cohort 3: RSV604 administered 72 hr post inoculation with RSV.
- Cohort 4: RSV604 administered 120 hr post inoculation with RSV.

Centers

United Kingdom (1)

Objectives:

Primary objective:

- To evaluate the antiviral activity of RSV604, given orally, on nasal RSV load, as measured by RT-PCR, in healthy adults experimentally inoculated with a challenge virus of RSV.
- To evaluate the safety of RSV604 when given on a 5-day regimen to RSV-infected healthy adults.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral administration of RSV604 of doses 150 mg, 300 mg, 450 mg and 600 mg.

Statistical Methods

The difference in primary end point (viral load AUC) between RSV604 treated groups and placebo was investigated by analysis of covariance with the baseline viral load as a covariate. Two-sided t tests for a treatment difference were reported. A similar analysis was done for the cumulative symptom score and the area under the nasal secretion curve.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Consenting male and female (not of child-bearing potential) subjects between the ages of 18 and 45 years, inclusive, were enrolled.
- Subjects were required to be healthy as determined by vital signs, medical history, ECG, laboratory tests and physical examination.

Exclusion criteria:

- Subjects with a history of prolonged QT-interval syndrome, abnormal serum K+ or Mg++ values were excluded from the study.

Participant Flow Table

Description	Number of Subjects
Enrolled	66
Discontinued	1
Reason for discontinuation	
Symptoms prior to medication	1
Evaluated	65

Baseline Characteristics

Demographic summary by treatment group

	Demographic Variable	C2: RSV604 N=16	C3: RSV604 N=9	C4: RSV604 N=12	Placebo/ No trt: N=28
Age (years)	n	16	9	12	28
	mean	25.6	28.3	26.1	26.0
	SD	5.37	6.34	3.90	5.57
	minimum	18	20	21	19
	median	26.0	26.0	25.5	24.5
	maximum	41	39	33	40
Height (cm)	n	16	9	12	28
	mean	174.8	178.9	177.8	177.5
	SD	8.05	10.47	8.85	6.50
	minimum	158	163	167	167
	median	174.5	177.0	176.0	177.5
	maximum	192	195	194	187
Weight (kg)	n	16	9	12	28
	mean	73.26	81.67	71.96	78.46
	SD	11.785	14.268	11.971	5.949
	minimum	52.0	65.0	56.0	69.0
	median	73.50	83.00	72.50	78.50
	maximum	101.0	110.0	92.0	96.0

Summary of Efficacy

Primary Outcome Result(s)

Summary and inferential statistics for 5 day viral AUC (log IU/mL*day)

Treatment Group	Statistic	N	Mean (std)	Range	P-value
Placebo or Untreated	Viral AUC in Days 2-6 post inoculation	28	14.3 (3.9)	(10.8 -23.8)	
	Viral AUC in Days 3-7 post inoculation	28	15.6 (5.4)	(10.8 -26.7)	
	Viral AUC in Days 5-10 post inoculation	11[1]	13.4 (4.5)	(10.8 -23.5)	
RSV604 C2	Viral AUC in Days 2-5 post inoculation	16	12.0 (2.1)	(10.8 -17.8)	0.0352[2]
RSV604 C3	Viral AUC in Days 3-7 post inoculation	9	18.9 (6.4)	(10.8 -28.6)	0.1379[3]
RSV604 C4	Viral AUC in Days 5-10 post inoculation	12	15.6 (5.2)	(10.8 -24.5)	0.2733[4]

1: Viral AUC in days 5-10 only computed on placebo subjects in Cohort 4.
2: two-sided p-value for comparison to pooled placebo/untreated viral AUC in days 2-6
3: two-sided p-value for comparison to pooled placebo/untreated viral AUC in days 3-7
4: two-sided p-value for comparison to Cohort 4 placebo viral AUC in days 5-10

Summary and inferential statistics for the area under nasal secretion weight curve

	N	Mean (mg*day)	SD (mg*day)	P=value[1]
Placebo/Untreated	28	24209	39866	N/A
RSV604 C2	16	3565	6028	0.052
RSV604 C3	9	20631	43005	0.786
RSV604 C4	12	29996	38973	0.626

[1]Two-sided p-value for a difference from the placebo/untreated group calculated by analysis of covariance with the nasal secretion weight at day 1 as a covariate

Refer to Safety Result section for primary outcome result.

Summary of Safety

Safety Results

Summary of adverse events by body system and preferred term

		RSV604 Cohort 2 N=16		RSV604 Cohort 3 N=9		RSV604 Cohort 4 N=12		Pooled placebo or untreated N=28	
Body system	**Adverse event (preferred term)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
- Any body system		11	(68.8)	8	(88.9)	12	(100)	19	(67.9)
Blood and lymphatic system disorders	- Total					1	(8.3)	2	(7.1)
	Lymphadenopathy							2	(7.1)
	Neutrophilia					1	(8.3)		
Ear and labyrinth disorders	- Total	1	(6.3)					1	(3.6)
	Ear pain	1	(6.3)					1	(3.6)
Gastrointestinal disorders	- Total	9	(56.3)	5	(55.6)	10	(83.3)	8	(28.6)
	Abdominal distension					1	(8.3)		
	Abdominal pain	2	(12.5)	2	(22.2)	6	(50.0)	1	(3.6)
	Aphthous stomatitis	1	(6.3)			3	(25.0)	2	(7.1)
	Diarrhoea	6	(37.5)	1	(11.1)	6	(50.0)	3	(10.7)
	Dyspepsia	3	(18.8)	3	(33.3)	3	(25.0)	2	(7.1)
	Faeces pale	1	(6.3)						
	Gastritis	1	(6.3)						
	Gingival bleeding	1	(6.3)						
	Nausea					3	(25.0)	1	(3.6)
	Painful defaecation			1	(11.1)				
	Paraesthesia oral			1	(11.1)				
	Reflux oesophagitis					2	(16.7)		
	Vomiting					1	(8.3)		
General disorders and administration site conditions	- Total	3	(18.8)	2	(22.2)	1	(8.3)	3	(10.7)
	Malaise	2	(12.5)	2	(22.2)	1	(8.3)	3	(10.7)
	Non-cardiac chest pain	2	(12.5)						
Infections and infestations	- Total	1	(6.3)						
	Gastroenteritis	1	(6.3)						

Body system	Adverse event (preferred term)	RSV604 Cohort 2 N=16 n	(%)	RSV604 Cohort 3 N=9 n	(%)	RSV604 Cohort 4 N=12 n	(%)	Pooled placebo or untreated N=28 n	(%)
Injury, poisoning and procedural complications	- Total							2	(7.1)
	Contusion							1	(3.6)
	Skin laceration							1	(3.6)
Investigations	- Total	1	(6.3)	1	(11.1)	1	(8.3)	1	(3.6)
	C-reactive protein increased					1	(8.3)		
	Gamma-glutamyltransferase increased	1	(6.3)						
	Transaminases increased			1	(11.1)	1	(8.3)	1	(3.6)
Metabolism and nutrition disorders	- Total					3	(25.0)		
	Anorexia					3	(25.0)		
Musculoskeletal and connective tissue disorders	- Total	1	(6.3)	1	(11.1)	6	(50.0)	3	(10.7)
	Arthralgia					2	(16.7)		
	Back pain			1	(11.1)	3	(25.0)		
	Muscle spasms							1	(3.6)
	Musculoskeletal pain					1	(8.3)	2	(7.1)
	Myalgia	1	(6.3)			1	(8.3)		
Nervous system disorders	- Total	3	(18.8)	3	(33.3)	6	(50.0)	8	(28.6)
	Anosmia							1	(3.6)
	Dizziness			1	(11.1)				
	Headache	1	(6.3)	3	(33.3)	3	(25.0)	6	(21.4)
	Paraesthesia	1	(6.3)						
	Presyncope	2	(12.5)			2	(16.7)		
	Sinus headache			1	(11.1)			1	(3.6)
	Somnolence					2	(16.7)		
Renal and urinary disorders	- Total			1	(11.1)				
	Dysuria			1	(11.1)				

Body system	Adverse event (preferred term)	RSV604 Cohort 2 N=16 n	(%)	RSV604 Cohort 3 N=9 n	(%)	RSV604 Cohort 4 N=12 n	(%)	Pooled placebo or untreated N=28 n	(%)
Respiratory, thoracic and mediastinal disorders	- Total	3	(18.8)	4	(44.4)	11	(91.7)	11	(39.3)
	Cough	2	(12.5)	1	(11.1)	2	(16.7)	1	(3.6)
	Dysphonia	1	(6.3)						
	Dyspnoea			1	(11.1)				
	Epistaxis					1	(8.3)	1	(3.6)
	Nasal congestion	1	(6.3)	1	(11.1)	4	(33.3)	8	(28.6)
	Oropharyngeal pain	2	(12.5)	2	(22.2)	4	(33.3)	3	(10.7)
	Pleuritic pain	1	(6.3)						
	Productive cough	1	(6.3)						
	Rhinorrhoea	1	(6.3)	2	(22.2)	8	(66.7)	9	(32.1)
	Rhonchi			1	(11.1)				
Skin and subcutaneous tissue disorders	- Total	1	(6.3)	1	(11.1)	1	(8.3)	3	(10.7)
	Dermatitis							1	(3.6)
	Hyperhidrosis					1	(8.3)		
	Pruritus	1	(6.3)						
	Rash							2	(7.1)
	Rash erythematous			1	(11.1)				
Vascular disorders	- Total					2	(16.7)	1	(3.6)
	Hot flush					2	(16.7)		
	Phlebitis							1	(3.6)

Serious Adverse Events by System Organ Class

No death, one serious AE and no other significant AE occurred in this study

Other Relevant Findings

None

Date of Clinical Trial Report

04-Jun-2010