LBA6

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial of Presatovir (GS-5806), an Oral RSV Fusion Inhibitor, for the Treatment of Respiratory Syncytial Virus Lower Respiratory Tract Infection in Hematopoietic-Cell Transplantation Recipients

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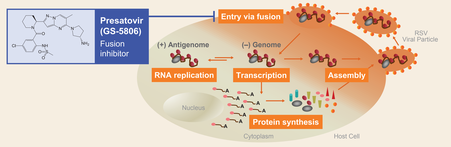
Introduction

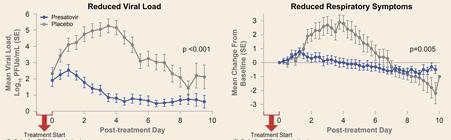
Respiratory Syncytial Virus (RSV)

- RSV is a significant cause of morbidity and mortality among children aged <5 y
  - Worldwide: ~3.4 million hospitalizations, with up to 200,000 deaths[1]
  - US: ~60,000 hospitalizations in infants aged <24 mo[2]
- RSV infections also cause significant morbidity and mortality in adults
  - Elderly with underlying cardiopulmonary disease (prevalence 5–8%); ~10,000 deaths each year among adults aged >50 y[3]
  - Immunocompromised: hematopoietic-cell transplant (HCT) and lung transplant patients (prevalence 2–17%); ~25% of upper respiratory tract infections (URTIs) progress to lower respiratory tract (LRT)[4]
- No effective treatment for RSV infection is available

Presatovir: Oral Small-Molecule RSV Fusion Inhibitor



Healthy Volunteer Model of RSV Infection[5]



PFUe, plaque-forming unit equivalent; SE, standard error.

- Dose-proportional low variability pharmacokinetics (PK); half-life ~33–35 h
- Concentrates in the lung
  - Extracellular lining fluid:plasma area under concentration-time curve ratio ~9.4 in multiple animal models
- Potent activity against RSV
  - Mean half-maximal effective concentration 0.4 nM for 75 clinical RSV (types A and B) isolates
  - 4-log reduction in RSV viral load, and significant reductions in signs and symptoms of RSV infection in human RSV challenge study[6]
- Favorable safety profile with ~500 adults dosed

Objectives

- **Primary:** to evaluate the effect of presatovir on RSV viral load in autologous and allogeneic HCT recipients with acute RSV LRT infection (LRTI)
- **Secondary:**
  - To evaluate the effects of presatovir on rates of respiratory failure and all-cause mortality
  - To evaluate the PK, safety, and tolerability of presatovir

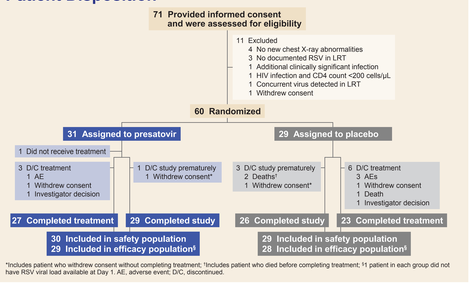
Methods

Study Design

- 60 RSV-positive patients with evidence of LRTI were randomized 1:1 to receive presatovir vs placebo
- **Stratification criteria:**
  - Supplemental O_2 requirement (≤ or >2 L/min) at time of randomization
  - Treatment of current RSV infection (yes or no) with ribavirin (RBV; oral, intravenous, or aerosolized)
- **Key assessments at each study visit:**
  - Bilateral nasal sampling for viral testing (RSV viral load, respiratory virus multiplex, and sequencing)
  - O_2 saturation assessment
  - Electrocardiograms (Days 1, 17, and 28)
  - Safety assessments and blood draws
- **Key inclusion criteria:**
  - Received autologous or allogeneic HCT using any conditioning regimen
  - Evidence of new abnormalities on chest X-ray obtained <48 h before screening and determined to be consistent with LRTI by local radiologist relative to most recent chest X-ray
  - RSV in both upper (eg, nasal swab, nasopharyngeal swab, or nasal wash) and lower (eg, induced sputum, bronchoalveolar lavage, or lung biopsy) respiratory tract as determined by local testing (eg, polymerase chain reaction [PCR], direct fluorescent antibody, respiratory viral panel assay, or culture)
    - All samples must have been collected ≤6 d before Day 1
- **Key exclusion criteria:**
  - Invasive mechanical ventilation required at time of randomization
  - Positive for other respiratory viruses (limited to influenza, parainfluenza, human rhinovirus, adenovirus, human metapneumovirus, and coronavirus) from LRT sample as determined by local testing
  - Inadequately treated, clinically significant bacteremia or fungemia ≤7 d before screening, or bacterial, fungal, or viral pneumonia ≤2 wk before screening
- **Endpoints:**
  - **Primary:** time-weighted average change in nasal RSV viral load from Days 1 to 9 (DAVG9) as measured by quantitative reverse transcription PCR (RT-qPCR)
  - **Secondary:**
    - Number of supplemental O_2-free days through Day 28
    - % of patients developing respiratory failure (of any cause) requiring mechanical ventilation (invasive or noninvasive) through Day 28
    - % of patients with all-cause mortality through Day 28
- **Statistical methods:**
  - **Efficacy:**
    - Primary efficacy analysis was evaluated in full analysis set (FAS), which included all randomized patients with RSV log_{10} viral load ≥ lower limit of quantitation of RT-qPCR assay in Day 1 nasal sample (determined by RT-qPCR at central lab) who received ≥1 dose of study drug
    - Primary endpoint was analyzed using a parametric analysis of covariance model with corresponding baseline RSV viral load and stratification factors as covariates
    - Secondary endpoints:
      - Number of supplemental O_2-free days through Day 28 was analyzed using a negative binomial model with stratification factors as covariates and an offset parameter to account for on-study duration
      - % of patients who developed respiratory failure requiring mechanical ventilation or with all-cause mortality was analyzed using Cochran-Mantel-Haenszel test, adjusting for stratification factors
    - All endpoints were analyzed using 2-sided tests for treatment differences
  - **Safety:** performed for all patients who received ≥1 dose of study drug and summarized by treatment using number (%) of patients with events/abnormalities for categorical data and descriptive statistics for continuous data

Results

Patient Disposition



*Includes patient who withdrew consent without completing treatment; †Includes patient who died before completing treatment; ‡1 patient in each group did not have RSV viral load available at Day 1. AE, adverse event; D/C, discontinued.

HCT-Related Demographics

		Presatovir, n=30	Placebo, n=29
Median age, y (IQR)		57 (40, 63)	55 (50, 63)
Median days from transplant to 1st dose (IQR)		451 (169, 863)	517 (182, 703)
HCT indications, n (%)	Acute leukemia	13 (43)	11 (38)
	Other	7 (23)	5 (17)
	Myeloma	5 (17)	6 (21)
	Lymphoma	5 (17)	5 (17)
	Chronic lymphocytic leukemia	0	2 (7)
	Aplastic anemia	0	1 (3)
Donor type, n (%)	Unrelated	18 (60)	15 (52)
	Matched-related	5 (17)	9 (31)
	Autologous	4 (13)	5 (17)
	Mismatched-related	3 (10)	0
Cell source, n (%)	Peripheral blood	25 (83)	25 (86)
	Bone marrow	4 (13)	2 (7)
	Cord blood	1 (3)	2 (7)
Acute or chronic graft-vs-host disease, n (%)	Yes	17 (57)	17 (59)
	No	9 (30)	7 (24)
	Not applicable, autologous	4 (13)	5 (17)

RSV-Related History

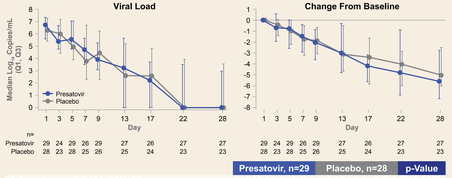
		Presatovir, n=30	Placebo, n=29
Hospitalized on 1st dosing date, n (%)		26 (87)	27 (93)
Median duration of RSV symptoms before 1st dose, d (IQR)		6 (4, 8)	5 (3, 7)
Mean baseline viral load, log_{10} copies/mL (SD)		6.2 (1.4)	6.0 (1.6)
RSV type, n (%)	RSV A	15 (50)	14 (48)
	RSV B	14 (47)	14 (48)
Received RBV, n (%)		12 (40)	11 (38)
Inhaled*		5	7
Oral*		5	3
Intravenous*		0	1

*From FAS. IQR, interquartile range; SD, standard deviation.

Mean Presatovir Exposure >4x $paEC_{95}$ for ≥21 Days*

*Circles, observed values; dotted line, 4x plasma-binding—adjusted effective concentration required to inhibit RSV replication by 95% ($paEC_{95}$).

Primary Endpoint: DAVG9 in Full Analysis Set



	Presatovir, n=29	Placebo, n=28	p-Value
Adjusted mean DAVG9 (95% CI)	-1.00 (-1.4, -0.6)	-0.97 (-1.4, -0.5)	0.94
Treatment difference (95% CI)	-0.02 (-0.62, 0.57)		

CI, confidence interval; Q, quartile.

Secondary Endpoints in Full Analysis Set

	Presatovir, n=29	Placebo, n=28	p-Value
Mean supplemental O_2-free days through Day 28 (SD)	21 (11.1)	20 (11.7)	0.84
Patients with respiratory failure through Day 28, n (%)	3 (10)	3 (11)	0.98
All-cause mortality through Day 28, n (%)	0 (0)	2 (7)	0.19

- Presatovir treatment had no significant effect on clinical endpoints

Effect of Need for Supplemental O_2 at Baseline

	Presatovir, n=19	Placebo, n=18	p-Value
Adjusted mean DAVG9 (95% CI)	-1.51 (-2.1, -1.0)	-1.15 (-1.7, -0.6)	0.35
Mean supplemental O_2-free days through Day 28 (SD)	27 (5)	23 (10)	0.16
Patients with respiratory failure through Day 28, n (%)	0	0	N/A
All-cause mortality through Day 28, n (%)	0	1 (6)	0.35
Supplemental O_2 >2 L/min	**Presatovir, n=10**	**Placebo, n=10**	**p-Value**
Adjusted mean DAVG9 (95% CI)	-0.40 (-1.2, 0.4)	-0.89 (-1.6, -0.1)	0.35
Mean supplemental O_2-free days through Day 28 (SD)	9 (11)	13 (12)	0.48
Patients with respiratory failure through Day 28, n (%)	3 (30)	3 (30)	0.98
All-cause mortality through Day 28, n (%)	0	1 (10)	0.36

N/A, not applicable.

- Presatovir-treated patients who did not require supplemental O_2 at baseline had numerically more supplemental O_2-free days

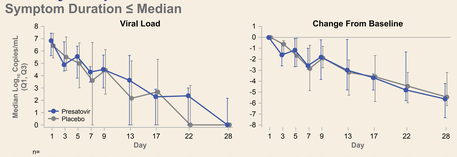
RBV Use Did Not Seem to Account for Lack of Presatovir Effect

RBV Prescribed at Baseline	Presatovir, n=10	Placebo, n=11	p-Value
Adjusted mean DAVG9 (95% CI)	-0.8 (-1.6, -0.01)	-0.6 (-1.4, 0.2)	0.64
Mean supplemental O_2-free days through Day 28 (SD)	18 (12)	22 (11)	0.50
Patients with respiratory failure through Day 28, n (%)	1 (10)	0	0.39
All-cause mortality through Day 28, n (%)	0	1 (9)	0.39
RBV Not Prescribed at Baseline	**Presatovir, n=19**	**Placebo, n=17**	**p-Value**
Adjusted mean DAVG9 (95% CI)	-1.2 (-1.7, -0.6)	-1.2 (-1.8, -0.7)	0.88
Mean supplemental O_2-free days through Day 28 (SD)	22 (11)	18 (12)	0.84
Patients with respiratory failure through Day 28, n (%)	2 (11)	3 (18)	0.74
All-cause mortality through Day 28, n (%)	0	1 (6)	0.35

- Of placebo-treated patients, those who did not receive RBV treatment experienced a faster decline in DAVG9

Primary Endpoint: DAVG9

Symptom Duration ≤ Median



	Presatovir, n=13	Placebo, n=16	p-Value
Adjusted mean DAVG9 (95% CI)	-1.47 (-2.2, -0.7)	-1.29 (-2.0, -0.6)	0.72
Treatment difference (95% CI)	-0.17 (-1.1, 0.8)		

Safety Summary

Patients, n (%)	Presatovir, n=30	Placebo, n=29
TEAE	24 (80)	23 (79)
Grade ≥3	7 (23)	9 (31)
Serious TEAE	7 (23)	7 (24)
Early drug D/C due to TEAE	1 (3)	3 (10)
Early study D/C due to TEAE	0	2 (7)
Treatment-emergent death	0	2 (7)

TEAE, treatment-emergent AE.

- No significant imbalance in TEAEs
- Presatovir-treated patients had fewer infection- and respiratory-related Grade ≥3 TEAEs
  - Infections and infestations: presatovir, n=1 (3%; influenza); and placebo, n=4 (14%; pneumonia, bacterial infection, febrile infection, and sepsis)
  - Respiratory, thoracic and mediastinal disorders: presatovir, n=1 (3%; respiratory failure); and placebo, n=4 (14%; respiratory failure, pulmonary embolism, and respiratory tract congestion)
- No significant imbalance in laboratory abnormalities

Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities

	Patients, n (%)	Presatovir, n=30	Placebo, n=29
Liver	Alanine aminotransferase >5x ULN	3 (10)	0
	Aspartate aminotransferase >5x ULN	1 (3)	0
	Alkaline phosphatase >5x ULN	1 (4)	0
	Bilirubin >2.5x ULN	0	1 (3)
Hematology	Hemoglobin <7.5 g/dL	8 (27)	9 (31)
	Leukocytes <1500/mm³	1 (3)	6 (21)
	Lymphocytes <500/mm³	6 (21)	8 (28)
	Neutrophils <750/mm³	1 (3)	7 (24)
	Platelets <50,000/mm³	6 (20)	4 (14)

ULN, upper limit of normal.

Postbaseline F-Gene Population Sequencing

Patients, n (% of FAS)	Presatovir, n=29	Placebo, n=28
With data	27 (93)	22 (79)
Any substitutions at resistance positions	6 (21)	0
Developed known resistance mutations to presatovir*	4 (14)	0
T400I	2	—
L141F	1	—
S398L	1	—
D486N	1	—
Fusion inhibitor resistance mutation†	1 (3)	0
D486E	1	—
Other substitution at known resistance position‡	1 (3)	0
D486V	1	—

*Mutations previously selected by presatovir treatment in clinical studies or in vitro and shown to reduce susceptibility to presatovir, including L138F/I, F140I/L, L141F/W, T325A, D338Y, S398L, K399I/N, T400A/I/V, I474T, D486N, E487D, F488L/S/Y, and N517I; †Mutations previously selected by or shown to reduce susceptibility to other RSV fusion inhibitors in vitro for which presatovir susceptibility is unknown, including G143S, V144A, D392G, K394R, D401E, D486E, F488I/V, and D489E/Y; ‡Amino-acid substitution at known fusion inhibitor resistance-associated positions for which presatovir susceptibility is unknown.

Primary and Secondary Endpoints by Resistance Status

	Presatovir		
	No resistance, n=23	Resistance, n=6	Placebo, n=28
Median DAVG9 (IQR)	-1.44 (-2.34, -0.78)	-0.34 (-0.49, 1.19)	-0.89 (-1.73, -0.18)
Median supplemental O_2-free days (IQR)	28 (25, 28)	3 (0, 6)	28 (9, 28)
Respiratory failure, n (%)	1 (4)	2 (33)	3 (11)
All-cause mortality, n (%)	0	0	2 (7)

Conclusions

- Presatovir exposure levels were well above 4x $paEC_{95}$ for desired duration
- Presatovir treatment had no significant impact on primary or secondary endpoints in patients with RSV infection with LRTI
  - Trends suggest that early treatment of less severely ill patients (those that do not require supplemental O_2) may be more effective
  - Lack of efficacy may be related to delayed treatment
- Presatovir was well tolerated, without evidence of any significant clinical or laboratory adverse effects
  - Presatovir-treated patients had fewer infection- and respiratory-related Grade ≥3 TEAEs
- RSV F-gene mutations were detected in 21% of presatovir-treated patients, but the clinical implications of this are unknown
- Presatovir treatment was not beneficial in HCT patients with documented RSV LRTI

References

1. Nair H, et al. Lancet 2010;375:1545-55; **2.** Hall CB, et al. N Engl J Med 2009;360:588-98; **3.** Thompson WW, et al. JAMA 2003;289:179-86; **4.** Kim Y-J, et al. J Infect Dis 2014;209:1195-204; **5.** DeVincenzo JP, et al. N Engl J Med 2014;371:711-22; **6.** See S, et al. Biol Blood Marrow Transplant 2013;19:589-96.

Acknowledgments

We extend our thanks to the patients and their families. This study was funded by Gilead Sciences, Inc.

Disclosures

F.M. Marty: Gilead, Alexion, Basilea, Chimerix, Fate, GSK, Merck, Roche, Shire, United Medical, Viatera; **R. Chemaly:** Gilead, Ablynx, Adama Biologics, Ansun Biopharma, Astellas, Chimerix, Janssen, Medicines Company, Novartis, Oxford Immunotec, Pulmotec, Workhard, Xenex; **A. Bergeron, D.-G. Lee, E. Blanchard, M. McKevitt, D. Porter, R. Jordan, Y. Guo, P. German, T. Watkins,** and **J.W. Chien:** Gilead; **R. Patron:** nothing to disclose; **P. Ljungman:** Gilead, Alpha, AiCuris, Astellas, Oxford Immunotec, Shire; **Y.-J. Kim:** Gilead, Celltrion, Janssen; **M. Boeckh:** Gilead, AbbVie, Astellas, Chimerix, Helocyte, MSD, Shire; **A. Waghmare:** Gilead, Aviragen; **K. Mullane:** Gilead, Astellas, Chimerix, Contrafect, Crestone, GSK, Leonard Merlin, Medtrimmune, MSD, NoVia, Sage, Shire, Synexis; **C. Small:** Gilead, GSK, MSD, ViW; **H.H. Hirsch:** Gilead, Chimerix, Novartis; **S.S. Dadwal:** Gilead, AiCuris, Ansun Biopharma, GSK, MSD, Oxford Immunotec, Shire.

Presented at BMT Tandem Meetings, February 21–25, 2018, Salt Lake City, Utah