Supplementary Information

Pediatric Drugs

CROCuS, A Phase 2 Study Evaluating the Antiviral Activity, Clinical Outcomes, and Safety of Rilematovir in Children Aged ≥28 Days and ≤3 Years With Acute Respiratory Tract Infection Due to Respiratory Syncytial Virus

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Supplementary Methods

Eligibility Criteria

Eligible patients could have been at risk for severe respiratory syncytial virus (RSV) disease. For example, patients could have been premature at birth (only for patients ≥3 months of age at screening) or had comorbid conditions, including bronchopulmonary dysplasia, Down syndrome, neuromuscular impairment, cystic fibrosis, recurrent wheezing/asthma (≥3 episodes of wheezing dyspnea since birth), congenital heart disease, or other congenital diseases.

Key Exclusion Criteria

Patients were not eligible if they were <3 months of age at screening and were born prematurely (ie, <37 weeks and 0 days of gestation), had major congenital anomalies or known cytogenetic or metabolic disorders that were not consistent with the underlying condition of RSV disease and/or present risk factor(s) for severe RSV disease as evaluated by the investigator (isolated open ductus arteriosus and open foramen ovale were not exclusionary as these are not considered major anomalies), were considered by the investigator to be immunocompromised within the past

12 months (whether due to underlying medical condition [eg, malignancy or genetic disorder other than immunoglobulin A deficiency, or known human immunodeficiency virus infection] or medical therapy [eg, immunomodulators other than corticosteroids for the treatment of comorbidities, chemotherapy, radiation, stem cell or solid organ transplant]), were being treated with extracorporeal membrane oxygenation (Cohort 1 only), were receiving chronic home oxygen therapy at screening, had other clinically significant abnormal electrocardiogram (ECG) findings not consistent with the present risk factor for severe RSV disease in the study population (as judged by the investigator based on the machine read ECG results at screening), had a QT interval corrected for heart rate according to Fridericia's formula (QTcF) interval >450 ms per the machine read (mean of triplicate) parameter result confirmed by repeat ECG recording during screening, had a personal or first- or second-degree family history of long QT syndrome or sudden cardiac death, or had evidence of one of the following ECG abnormalities per the machine read ECG result confirmed by repeat ECG recording at screening: repetitive premature ventricular contractions (>10/min), second- or third-degree heart block, complete or incomplete left bundle branch block or complete right bundle branch block. Participants were also not eligible if aged <3 months at time of screening and their mother received an investigational RSV vaccination during the pregnancy.

Time to End of Oxygen Supplementation

Time to end of oxygen supplementation up to 72 hours from first hospital discharge was derived as time (hours) from first dose of study treatment to last end date/time of any oxygen supplementation received, up to and including 72 hours following the patient’s first hospital discharge. This excluded oxygen supplementation received during rehospitalizations that occurred >72 hours after first hospital discharge.

Safety

Protocol-defined adverse events (AEs) of interest included cardiac events related to QT prolongation and hepatobiliary events (ie, increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], or transaminase levels or hypertransaminasemia).

Viral Sequencing Analyses

Genetic variations were defined as changes from reference sequence RSV-A Long (GenBank Accession number AY911262) or RSV-B strain 9320 (GenBank Accession number AY353550) for RSV-A and RSV-B samples, respectively. Genetic variations were analyzed with a next generation sequencing (NGS) read frequency of ≥3%. Baseline substitutions were defined as amino acid substitutions detected at baseline with an NGS read frequency of ≥15%. Emerging substitutions were defined as amino acid substitutions detected postbaseline with an NGS read frequency of ≥15% but not present at baseline (read frequency <3%). The list of 24 fusion (F) protein positions of interest was used for both RSV-A and RSV-B sequencing analyses and was defined based on in vitro selection experiments, clinical observations, and/or in vitro reduced susceptibility to RSV F inhibitors [1, 2]. This list includes the RSV F protein positions of specific interest for rilematovir (positions 141, 143, 394, 398, 400, 486, 488, and 489), based on in vitro selection experiments with rilematovir and/or in vitro reduced susceptibility to rilematovir [1].

Statistical Analysis

For Multiple Comparison Procedure-Modeling (MCP-Mod), 3 candidate models were used, covering a range of possible dose-response curves (linear, E_{max}, or exponential). Area under the curve (AUC) values with corresponding covariance matrix were determined by modeling $\log_{10}$ viral load values over time using a restricted maximum likelihood-based repeated measures approach. The model included fixed, categorical effects of treatment, strata, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline $\log_{10}$ viral load and baseline $\log_{10}$ viral load by-visit interaction. An unstructured (co)variance structure was used to model within-patient errors over time. Each of the candidate dose-response curves was tested using the corresponding contrast *t* test statistic, employing a critical value derived for the maximum of the *t* test statistics (based on the associated multivariate t-distribution) to ensure appropriate multiplicity correction that preserves the type I error rate. A positive dose-response trend was established when the maximum of the *t* test statistics exceeded the critical value.

Supplementary Results

Baseline Viral Sequencing Results

At baseline, amino acid substitutions among the 24 RSV F protein positions of interest were detected in 2.2% (5/226) of patients with sequencing data available in the combined cohort and included V127I in 4 patients (2, 1, and 1 in the rilematovir low dose, high dose, and placebo group, respectively) and V127L in 1 placebo-treated patient.

Safety

No emergent cardiac AEs related to QT prolongation were reported in either cohort. In Cohort 1, QTcF interval change abnormalities (ie, QTcF interval change from baseline of >60 ms) were reported for 2.1% of patients in the placebo group. No QTcF interval change abnormalities were reported in Cohort 2. No emergent QTcF interval >500 ms was reported in the study.

In Cohort 1, increased ALT and increased AST levels were reported as AEs in 2.1% of patients in the rilematovir high dose group, while hypertransaminasemia and increased transaminase levels were each reported in 2.0% of patients receiving placebo and were considered possibly related to study treatment by the investigator. In Cohort 2, an AE of increased ALT was reported for 2.9% of patients in the rilematovir low dose group. In both cohorts, hepatobiliary AEs corresponded to reported laboratory abnormalities, most patients recovered, and most events were considered not related to study treatment.

Supplementary Tables

Supplementary Table 1. Pre-planned Interim Analyses and Adaptive Design Elements[a]

Pre-planned IAs	Description
IA1	• Evaluate safety profile of Cohort 1 data and, if favorable, start enrollment of Cohort 2 (independent data monitoring committee recommendation) • Planned when ≥36 hospitalized patients in Cohort 1 had completed Day 14 assessments or had discontinued prior to Day 14
IA2	• Futility check and possible population enrichment[b] • Planned when approximately 70 to 80 hospitalized patients from Cohort 1 had completed Day 14 assessments or had discontinued prior to Day 14
IA3	• Sample size re-estimation for Cohort 2, futility check, and possible population enrichment[b] • Planned to be conducted when approximately 70 to 80 outpatients from Cohort 2 had completed Day 14 assessments or had discontinued prior to Day 14
IA4	• Futility check and possible population enrichment[b] • Planned to be conducted when approximately 150 outpatients from Cohort 2 had completed Day 14 assessments or had discontinued prior to Day 14

IA, interim analysis.

[a]During and after all interim analyses, investigators, patients, and local sponsor representatives remained blinded to treatment allocation.

[b]Analysis of data from subgroups based on time since symptom onset was performed to determine whether population enrichment should occur to limit enrollment to patients with ≤3 days since symptom onset. Decision for population enrichment could only occur once.

Supplementary Table 2. Study Cohorts and Treatment Groups

	Cohort 1, hospitalized patients			Cohort 2, outpatients		
	Age group 1: ≥28 days and <3 months	**Age group 2:** ≥3 months and <6 months	**Age group 3:** ≥6 months and ≤3 years	**Age group 1:** ≥28 days and <3 months	**Age group 2:** ≥3 months and <6 months	**Age group 3:** ≥6 months and ≤3 years
Total daily rilematovir dose[a]						
Rilematovir low dose, mg/kg	1.7	2.0	3.0	1.7	2.0	3.0
Min, max volume, mL	0.125, 0.725	0.125, 0.850	0.200, 1.300	0.125, 0.725	0.125, 0.850	0.200, 1.300
Rilematovir high dose, mg/kg	5.0	6.0	9.0	5.0	6.0	9.0
Min, max volume, mL	0.300, 2.200	0.375, 2.600	0.550, 4.000	0.300, 2.200	0.375, 2.600	0.550, 4.000
Placebo, mg/kg	-	-	-	-	-	-
Min, max volume for rilematovir low dose match, mL	0.125, 0.725	0.125, 0.850	0.200, 1.300	0.125, 0.725	0.125, 0.850	0.200, 1.300
Min, max volume for rilematovir high dose match, mL	0.300, 2.200	0.375, 2.600	0.550, 4.000	0.300, 2.200	0.375, 2.600	0.550, 4.000

The conversion of mg/kg dose to volume of rilematovir oral suspension was done by the Interactive Web Response System and communicated to the sites.

Placebo patients received an equivalent volume.

[a]The same total daily dose was administered after Protocol Amendment 4 but was divided into two doses (with twice daily administration of rilematovir).

Supplementary Table 3. PRESORS ObsRO v7.1 Signs and Symptoms of RSV and Definitions of Resolved/Not Resolved

PRESORS ObsRO v7.1 Signs and Symptoms of RSV	Definition of 'resolved'	Definition of 'not resolved'
Sleep disturbance	• As usual • A little more restless or disturbed than usual	• A lot more restless or disturbed than usual • Unable to sleep at all
Crying	• Crying as much as usual • More crying or fussier than usual, but calmed if held or soothed	• A lot more crying or fussier than usual; difficult to calm if held or soothed • Crying or fussy most of the time even if held or soothed
Activity level/illness behavior	• Appeared well • Less active • Less interested in playing or toys • Tired more easily	• Clinging or had to be held or carried • Not responding as usual • Floppy or limp
Breathing problems[a]	• None	• Gasping for air • Nostrils flaring • Head bobbed back and forth when breathing
Nasal secretions	• No stuffy or runny nose • Runny or stuffy nose that did not cause problems	• Breathing through mouth due to stuffy or runny nose • Stuffy or runny nose that caused problems eating, drinking, sleeping, or breathing
Tachypnea[a]	• None	• Breathing faster than usual
Tachycardia[a]	• None	• Heart beating faster than usual when resting
Retractions[a]	• None	• Belly sucked in when breathing in • Ribs more visible than usual when breathing in • Collarbone more visible than usual when breathing in • Skin at the base of throat sucked in when breathing in
Breathing sounds[a]	• Did not hear any of these sounds	• Crackling, rattling, or clicking • Snoring sounds even when awake • Whistling or wheezing sounds • Grunting

Cough[a]	• No coughing • Some coughing, but no problems resulting from coughing	• Some coughing with at least one problem caused by coughing (eg, gagging) • Coughing a lot • Coughing almost all of the time
Feeding problems	• As usual • A little less than usual	• A lot less than usual • Very little or vomited most of what was eaten/drank
Dehydration	• None • Dry skin or lips	• Dark yellow urine • Less urine • Sunken eyes • Sunken anterior fontanelle

ObsRO, Observer-Reported Outcome; PRESORS, Pediatric Respiratory Syncytial Virus Electronic Severity and Outcome Rating System; RSV, respiratory syncytial virus.

[a]PRESORS ObsRO key symptoms of RSV.

Supplementary Table 4. MCP-Mod Analysis of the Estimated AUC of RSV RNA Log_{10} Viral Load Through Day 5 in the ITT-i Analysis Population for Cohort 1 and Cohort 2[a] Combined

Candidate model	Z-statistic	Adjusted p-value
Emax (0.40428)	1.9610	0.047
Exponential (0.36411)	0.9240	0.279
Linear	1.4560	0.127

AUC, area under the curve; ITT-i, intent-to-treat-infected; MCP-Mod, multiple comparison procedure modeling; RNA, ribonucleic acid; RSV, respiratory syncytial virus.

[a]MCP-Mod analysis performed on the estimated AUC through Day 5, based on the primary analysis. Candidate models are given by E_{max} (0.40428), Exponential (0.36411) and Linear model. One-sided p-values are presented.

Supplementary Table 5. AUC Through Day 5 Based on Mixed Model for RSV RNA Log_{10} Viral Load in the ITT-i Analysis Population for Cohort 1 and Cohort 2 Combined[a]

	Placebo (n=79)	Rilematovir low dose (n=80)	Rilematovir high dose (n=72)
Mean RSV viral load AUC (95% CI) through Day 5	22.74 (21.677, 23.800)	21.48 (20.402, 22.566)	21.51 (20.374, 22.650)
Difference vs placebo in mean RSV viral load AUC (95% CI) through Day 5		−1.25 (−2.672, 0.164)	−1.23 (−2.679, 0.227)
Difference: combined rilematovir vs placebo in mean RSV viral load AUC (95% CI) through Day 5	−1.24 (−2.479, −0.001)		

AUC, area under the curve; CI, confidence interval; ITT-i, intent-to-treat-infected; RNA, ribonucleic acid; RSV, respiratory syncytial virus.

[a]The analysis model included fixed (discrete) effect parameters for treatment groups, randomization stratification factors (derived based on electronic case report form data), analysis visit and treatment-by-analysis visit interactions, as well as continuous covariates for baseline log_{10} viral load and baseline log_{10} viral load-by-analysis visit interactions.

Supplementary Table 6. Summary of Medical Resource Utilization During Study Treatment and Follow-up

	Placebo	Rilematovir low dose	Rilematovir high dose
Cohort 1, n	**47**	**47**	**44**
Patients re-hospitalized, n (%)	3 (6.4)	2 (4.3)	1 (2.3)
Primary reason for rehospitalization			
AE	3 (6.4)	2 (4.3)	1 (2.3)
RSV-related complication	0	1 (2.1)	1 (2.3)
Non–RSV-related complication	3 (6.4)	1 (2.1)	0
Patients with outpatient medical care encounters, n (%)	9 (19.1)	6 (12.8)	9 (20.5)
Cohort 2, n	**32**	**33**	**28**
Patients with medical care encounters, n (%)	3 (9.4)	5 (15.2)	7 (25.0)
Patients with hospital inpatient encounters	2 (6.3)	2 (6.1)	4 (14.3)
Patients hospitalized due to RSV-related respiratory conditions	1 (3.1)	1 (3.0)	1 (3.6)
Patients with outpatient medical care encounters, n (%)	2 (6.3)	3 (9.1)	4 (14.3)

AE, adverse event; RSV, respiratory syncytial virus.

Supplementary Table 7. Summary of Emergent RSV-related Complications[a]

Patients with event, n (%)	Cohort 1			Cohort 2		
	Placebo (n=47)	**Rilematovir low dose (n=47)**	**Rilematovir high dose (n=44)**	**Placebo (n=32)**	**Rilematovir low dose (n=33)**	**Rilematovir high dose (n=28)**
Emergent RSV-related complications	7 (14.9)	6 (12.8)	9 (20.5)	3 (9.4)	1 (3.0)	4 (14.3)
RSV-related respiratory complications	6 (12.8)	4 (8.5)	8 (18.2)	1 (3.1)	1 (3.0)	3 (10.7)
Grade ≥3 RSV-related complications	3 (6.4)	3 (6.4)	1 (2.3)	1 (3.1)	0	1 (3.6)

RSV, respiratory syncytial virus.

[a]RSV-related complications were identified based on reported adverse events coded using the Medical Dictionary for Regulatory Activities version 23.1.

Supplementary Table 8. Summary of Sequencing Data for Patients With Emerging Amino Acid Substitutions Considering the 24 F Protein Positions of Interest (ITT-i Analysis Population)

Patient	Cohort	Treatment group	Visit	RSV RNA viral load (log_{10} copies/mL)	RSV subtype	Baseline/emerging amino acid substitutions at 24 positions of interest (NGS read frequency)[a]
1	Cohort 1	Rilematovir high dose	Baseline	5.41	B	None
			Day 2	7.15	B	None
			Day 3	5.93	B	None
			Day 5	4.56	B	None
			Day 6	4.61	B	None
			Day 7	4.60	B	D338Y (25.2%)
			Day 9	5.08	B	D338Y (43.5%)
			Day 10	4.24	B	None
2	Cohort 1	Rilematovir high dose	Baseline	5.61	A	None
			Day 2	4.75	A	Amplification failed
			Day 4	7.72	A	None
			Day 5	4.71	A	None
			Day 14	4.54	A	K399N (36.4%)
3	Cohort 2	Rilematovir high dose	Baseline	8.33	A	None
			Day 2	8.38	A	None
			Day 3	7.08	A	None
			Day 4	4.39	A	None
			Day 5	5.55	A	None
			Day 8	4.17	A	G143S (55.5%)
4	Cohort 2	Rilematovir high dose	Baseline	7.12	B	None

	Day 7	4.30	B	G143S (58.4%)
	Day 12	4.29	B	G143S (41.9%)

ITT-i, intent-to-treat-infected; NGS, next generation sequencing; RNA, ribonucleic acid; RSV, respiratory syncytial virus.

[a]Baseline substitutions were defined as amino acid substitutions detected at baseline with an NGS read frequency of ≥15%. Emerging substitutions were defined as amino acid substitutions detected post-baseline with an NGS read frequency of ≥15% but not present at baseline (read frequency <3%).

Supplementary Table 9. Summary of Acceptability and Palatability of Rilematovir by Cohort in the ITT-i Analysis Population[a]

	Cohort 1			Cohort 2		
	Placebo n=47	**Rilematovir low dose n=47**	**Rilematovir high dose n=44**	**Placebo n=32**	**Rilematovir low dose n=33**	**Rilematovir high dose n=28**
Categorical response,[b] n	34	32	37	24	21	21
Child took medicine easily, n (%)	23 (67.6)	27 (84.4)	27 (73.0)	17 (70.8)	19 (90.5)	18 (85.7)
Disgusted expressions after tasting medicine, n (%)	7 (20.6)	3 (9.4)	5 (13.5)	2 (8.3)	2 (9.5)	3 (14.3)
Cried after tasting medicine, n (%)	4 (11.8)	0	1 (2.7)	2 (8.3)	0	2 (9.5)
Would not open mouth or turned head away to avoid medicine, n (%)	2 (5.9)	4 (12.5)	6 (16.2)	3 (12.5)	2 (9.5)	1 (4.8)
Spit out or coughed out medicine, n (%)	3 (8.8)	0	3 (8.1)	4 (16.7)	1 (4.8)	0
Gagged, n (%)	1 (2.9)	0	1 (2.7)	3 (12.5)	0	0
Vomited within 2 minutes of swallowing medicine, n (%)	1 (2.9)	0	0	0	0	0
Binary response,[c] n	34	32	37	24	21	21
Partly or not acceptable (No), n (%)	11 (32.4)	5 (15.6)	10 (27.0)	7 (29.2)	2 (9.5)	3 (14.3)
Acceptable (Yes), n (%)	23 (67.6)	27 (84.4)	27 (73.0)	17 (70.8)	19 (90.5)	18 (85.7)
95% Wilson score confidence interval[d]	(50.8, 80.9)	(68.2, 93.1)	(57.0, 84.6)	(50.8, 85.1)	(71.1, 97.3)	(65.4, 95.0)

ITT-i, intent-to-treat-infected.

[a]Caregivers' assessment of study drug acceptability and palatability was captured at Day 8 in response to the question 'In general, how did the child react when he/she was given the medicine?'

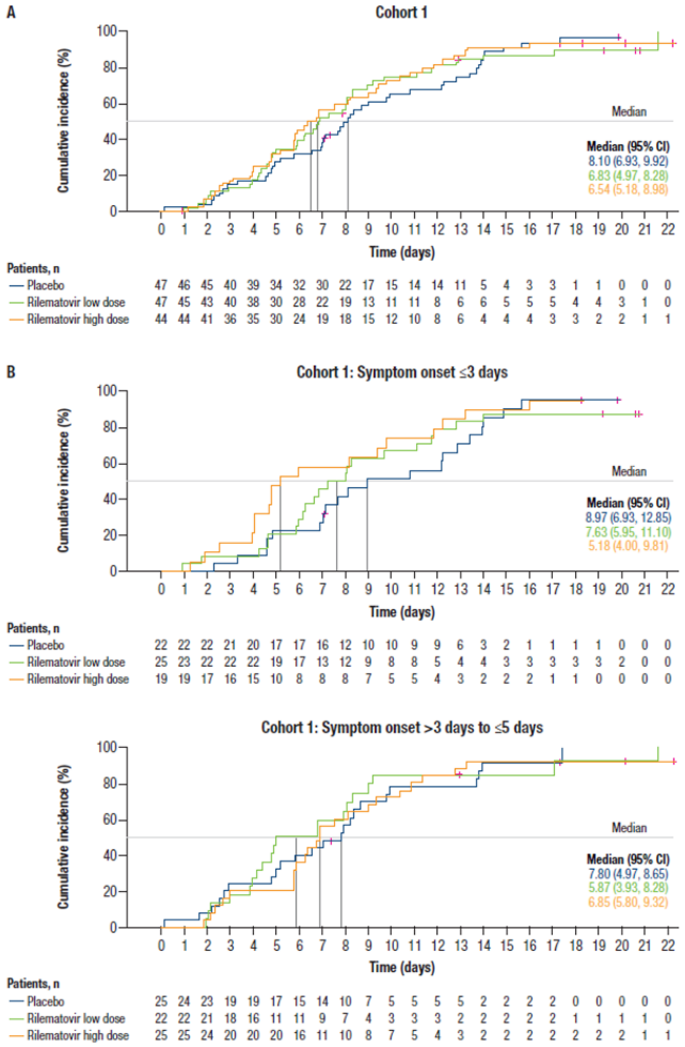
[b]Patients were counted in each selected category since they may have experienced one or more reactions to study drug administration. Consequently, the sum of percentages may be >100%.

[c]Drug was listed as acceptable only if the caregiver answered, 'child took medicine easily'.

[d]95% confidence interval for the binomial proportion of those who indicated the medication was acceptable versus those who did not.

Supplementary Figures

Supplementary Fig. 1 Time to resolution[a] of key RSV symptoms in Cohort 1 after free of supplementation for at least 24 hours (A) overall and (B) for patients in Cohort 1 randomized within ≤3 days or >3 days to ≤5 days since symptom onset.



RSV, respiratory syncytial virus.

[a]Defined as the time (hours) from first dose of study treatment until the first time at which all key RSV symptoms were scored as not present or mild (ie, "resolved") after being free of oxygen, hydration, and feeding supplementation for at least 24 hours.

+ indicates censoring.

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