Efficacy and Safety of Zapnometinib in Hospitalized Adult Patients with COVID-19: A Randomized, Double-blind, Placebo-controlled, Multi-center, Phase 2 Trial (RESPIRE)

Abstract 350

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Background

- Activation of MEK (mitogen-activated protein kinase kinase) is needed for replication of RNA viruses such as influenza, hantaviruses, RSV, and coronaviruses, [1,2] and overactivation of MEK pathways promotes the development of the "cytokine storm" [3]
- Zapnometinib (ATR-002) is an orally bioavailable, highly specific, small molecule inhibitor of MEK1 / MEK2 with immunomodulatory and antiviral properties
- Preclinical data show that zapnometinib modulates the pro-inflammatory host response, preventing the cytokine storm and associated morbidity, while also inhibiting viral propagation to reduce viral load [4–6]
- Zapnometinib was under development as a treatment for influenza at the time of SARS-CoV-2 outbreak; its immunomodulatory properties plus broad acting antiviral activity suggested it may be an effective treatment for COVID-19

Study design

- RESPIRE (NCT04776044) was a randomized, double-blind, placebo-controlled, proof-of-concept / Phase 2 trial in adults with moderate-to-severe COVID-19 requiring hospitalization (clinical severity status [CSS] 3 or 4). Those requiring ICU admission, high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation were excluded
- The primary endpoint was CSS at Day 15, measured on a 7-point ordinal scale based on WHO recommendations for trials of COVID-19 therapies [7] (Table 1)
- Patients were randomized 1:1 to oral zapnometinib (900 mg on Day 1; 600 mg daily on Days 2 – 6) or matching placebo, on top of standard of care therapy according to local guidelines (Figure 1)
- Randomization was stratified by trial sites and by CSS at baseline (3 or 4) within trial sites
- Time from randomization to discharge from hospital (TTHD) was the key secondary endpoint

Results

- The trial was terminated early in June 2022 as the success of global vaccination programs and prevalence of the Omicron variant increasingly impacted recruitment
- At termination, approximately half (104) of the planned 220 patients had been randomized, 103 were treated, and 101 were included in the full analysis set (zapnometinib: n=50; placebo: n=51), defined as patients who received at least one dose of investigational medical product and had at least one post-baseline measurement of the primary endpoint
- Baseline CSS was well balanced between arms: 40.0% of patients on zapnometinib and 41.2% on placebo had a CSS of 4 (Table 2)

Safety

- Zapnometinib was safe and well tolerated, and the frequency of adverse events was low and similar between zapnometinib and placebo (Table 3). Most TEAEs were mild or moderate in intensity; seven (6.8%) patients experienced a severe TEAE, more frequently in the placebo arm
- Three patients died during the trial (two in the placebo arm and one in the zapnometinib arm; all before day 30)

Primary endpoint

- On Day 15, patients on zapnometinib had higher odds of improved CSS vs placebo (odds ratio [OR] 1.54 [95% CI 0.72 – 3.33]; p=0.262; Figure 2). Data were similar in the per protocol set (n=98; OR 1.45 [95% CI: 0.67 – 3.17]; p=0.346), defined as patients from the full analysis set who did not have major protocol deviations
- Predefined subgroups analyses identified a trend for improvement in CSS in patients with severe disease at baseline (CSS 4; OR 2.57 [95% CI: 0.76 – 8.88]; p=0.128) and non-Omicron variants (OR 2.36 [95% CI: 0.85 – 6.71]; p=0.098)

Secondary endpoints

- The rate ratio for the key secondary endpoint (TTHD) was not significantly different between arms (1.31 [95% CI: 0.81 – 2.13]; p=0.274; Figure 3)
- A greater reduction in the time from randomization to hospital discharge was observed with zapnometinib versus placebo among patients with CSS 4 at baseline (rate ratio 1.59 [95% CI: 0.73 – 3.57]; p=0.245), equivalent to ~1.5 days shorter

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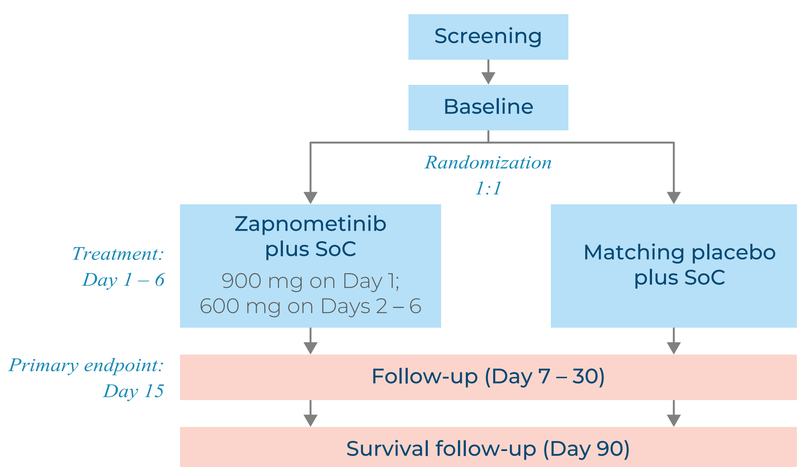
Table 1 Clinical severity status (primary endpoint) – Assessed on a 7-point scale

Patient state	CSS
Not hospitalized, no limitations of activities	1
Not hospitalized, limitations of activities	2
Hospitalized, not requiring supplemental oxygen	3
Hospitalized, requiring supplemental oxygen	4
Hospitalized, on non-invasive ventilation or high flow oxygen devices	5
Hospitalized, on invasive mechanical ventilation or ECMO	6
Death	7

ECMO, extracorporeal membrane oxygenation

Figure 1 RESPIRE study design



SoC standard of care

Table 2 Baseline demographics and disease characteristics

	Zapnometinib (n = 50)	Placebo (n = 51)	Total (n = 101)
Gender, n (%)			
Female	17 (34.0)	26 (51.0)	43 (42.6)
Male	33 (66.0)	25 (49.0)	58 (57.4)
Age, years			
Mean (SD)	54.1 (18.6)	56.8 (15.6)	55.4 (17.1)
Median (IQR)	54.5 (32.0)	57.0 (24.0)	56.0 (26.0)
Race, n (%)			
Asian	21 (42.0)	22 (43.1)	43 (42.6)
Black / African American	3 (6.0)	2 (3.9)	5 (5.0)
White	26 (52.0)	27 (52.9)	53 (52.5)
CSS, n (%)			
3 (hospitalized, not requiring supplemental O_2)	30 (60.0)	30 (58.8)	60 (59.4)
4 (hospitalized, requiring supplemental O_2)	20 (40.0)	21 (41.2)	41 (40.6)
SARS-CoV-2 variant			
Non-Omicron	27 (54.0)	29 (56.9)	56 (55.4)
Omicron	23 (46.0)	22 (43.1)	45 (44.6)
Median time since hospitalization, days (IQR)	2.0 (1.0)	2.0 (1.0)	2.0 (1.0)
Median time since symptom onset , days (IQR)	7.0 (6.0)	7.0 (5.0)	7.0 (5.0)
COVID-19 symptoms, n (%)			
Cough	46 (92.0)	48 (94.1)	94 (93.1)
Dyspnea	28 (56.0)	33 (64.7)	61 (60.4)
Fever	41 (82.0)	36 (70.6)	77 (76.2)

CSS, clinical severity status; IQR, interquartile range; SD, standard deviation

Conclusions

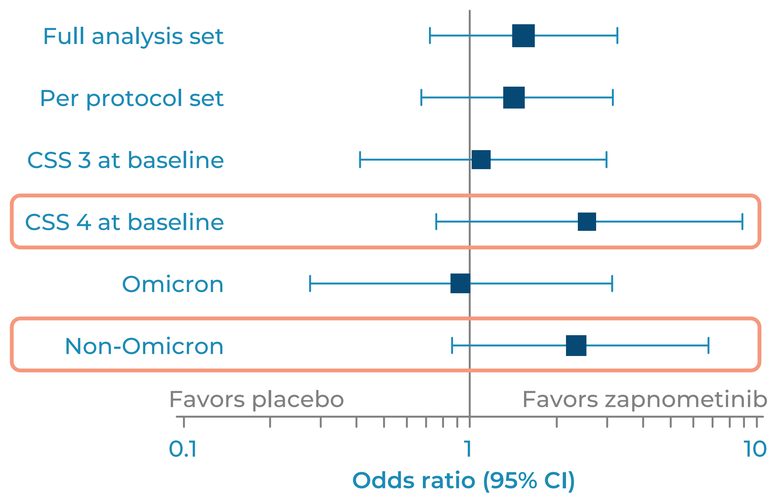
- Zapnometinib was safe and well tolerated in hospitalized patients with COVID-19
- Despite early termination of the trial, there were consistent trends for better outcomes with zapnometinib across the various efficacy endpoints, particularly in patients with severe disease / SARS-CoV-2 variants
- Hospital length of stay was shorter with zapnometinib in patients with more severe disease
- These results provide proof-of-concept for the innovative approach of targeting the intracellular Raf/MEK/ERK signaling pathway in patients with severe viral respiratory infections
- Further investigation of zapnometinib is justified – a Phase 2 trial is currently in preparation in hospitalized patients in need of oxygen with severe disease caused by influenza virus

Table 3 Summary of safety

Number of patients with: n (%)	Zapnometinib (n = 51)	Placebo (n = 52)	Total (n = 103)
Any TEAEs	20 (39.2)	18 (34.6)	38 (36.9)
TEAEs occurring in >5% of either			
ALT increased	3 (5.9)	1 (1.9)	4 (3.9)
Diarrhea	4 (7.8)	3 (5.8)	7 (6.8)
Any severe TEAE	2 (3.9)	5 (9.6)	7 (6.8)
Severe TEAEs occurring in >5% of either			
Dyspnea		3 (5.8)	3 (2.9)
Any serious TEAE	3 (5.9)	4 (7.7)	7 (6.8)
Serious TEAEs occurring in >5% of either			
None			
Any TEAE leading to discontinuation of IMP	1 (2.0)		1 (1.0)
Any TEAE leading to withdrawal from trial	1 (2.0)	2 (3.8)	3 (2.9)
Any ADR	11 (21.6)	8 (15.4)	19 (18.4)
ADRs occurring in >5% of either			
ALT increased	3 (5.9)	1 (1.9)	4 (3.9)
Diarrhea	3 (5.9)	1 (1.9)	4 (3.9)
Any severe ADR	1 (2.0)		1 (1.0)
Any serious ADR	2 (3.9)		2 (1.9)
Death	1 (2.0)	2 (3.8)	3 (2.9)

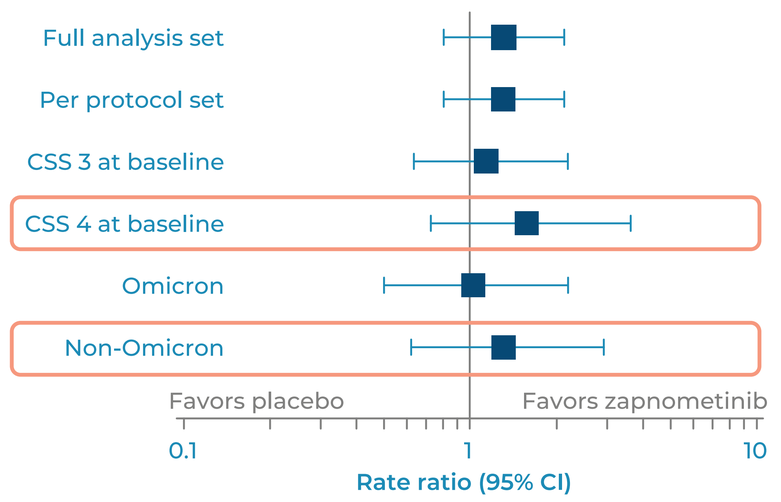
ADR, adverse drug reaction; ALT, alanine aminotransferase; IMP, investigational medicinal product; TEAE, treatment-emergent adverse event

Figure 2 Forest plot of odds ratios for CSS overall and in pre-planned subgroup analyses



CI, confidence interval; CSS, clinical severity status

Figure 3 Forest plot of rate ratios for time from randomization to discharge from hospital overall and in pre-planned subgroup analyses



CI, confidence interval; CSS, clinical severity status

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