MEK inhibition with zapnometinib as a treatment for RNA virus infections: The dual benefit of host immunomodulation and antiviral activity

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Introduction/Background

Zapnometinib (ATR-002) is a highly specific small-molecule inhibitor of MEK1 and MEK2. MEK inhibition downregulates the expression of cytokines and chemokines that cause hyperinflammatory host immune responses seen in some severe viral infections. The Raf/MEK/ERK host cell signaling pathway is essential for replication of many RNA viruses like Influenza virus, SARS-CoV-2, DENV and RSV.

We had previously reported results from the first clinical study (Phase 2 trial "RESPIRE") for zapnometinib in hospitalized patients with moderate to severe COVID-19[1]. Here we extend these data by providing results for the antiviral and immunomodulatory activity and the primary endpoint of the trial in the as treated patient population, analyzed separately for clinical severity at baseline (CSS 3 or 4) and virus type (Omicron vs. non-Omicron). Additional preplanned analyses (including worst CSS status over the whole study duration), and results for the key secondary endpoint (time to hospital release) are also provided.

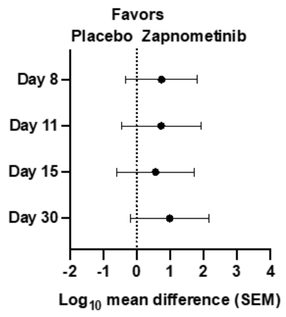
Methods

All methods used in this study are described in the clinical trial protocol provided by NCT04776044.

Access: https://clinicaltrials.gov →

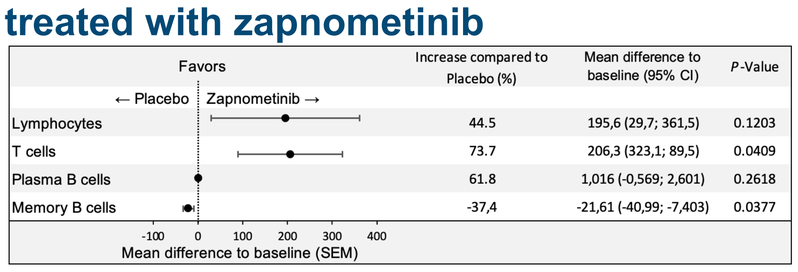
Results

Figure 1: Zapnometinib treatment favors viral load reduction to placebo (> 0.5 log_{10})



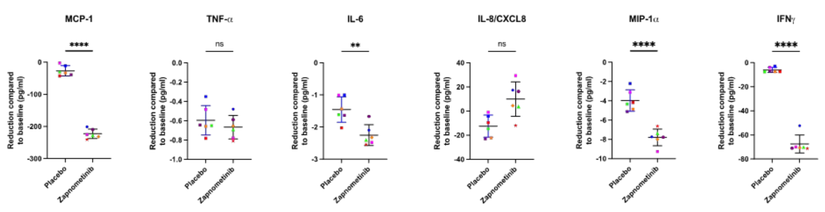
RNA virus titer mean change from baseline ± SEM over time in SARS-CoV-2 sputum samples from hospitalized COVID-19 patients on D8, D11, D15 and D30. Analysis only includes patients with baseline sputum SARS-CoV-2 RNA titer ≥ 500 copies/ml.

Figure 2: Increase of T cells in patients treated with zapnometinib



Mean difference ± SEM of the number of lymphocytes, T cells, Plasma B cells and Memory B cells compared to baseline in zapnometinib (n = 34) and placebo treated (n = 34) patients. The graphics represent values from the entire study period (D1, D3, D5, D8, D11, D15 and D30). The data were analyzed by one-tailed t-test.

Figure 3: Reduction of pro-inflammatory cytokines/chemokines with zapnometinib

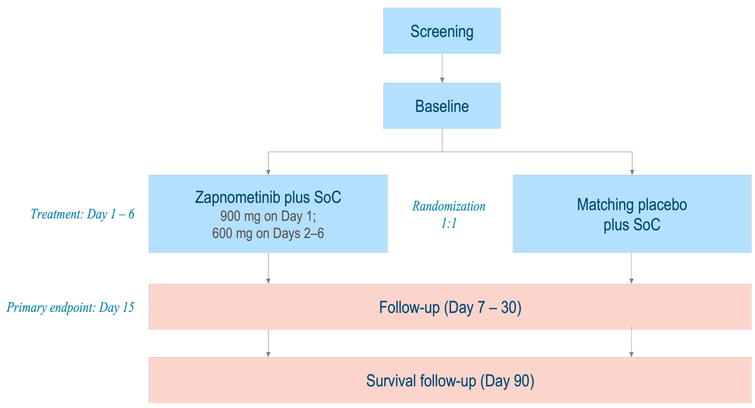


Reduction of cytokine and chemokine expression compared to baseline values. Analysis was performed with 6 patients from each group. All of them received either no standard of care treatment or antiviral treatment. Patients that received glucocorticoids as standard of care were excluded. Analysis was performed with values from the complete observation period (until day 30), horizontal line showing the mean value ± SEM of all days.

Phase 2 Clinical Study Design ("RESPIRE")

- 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
- 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

Figure 4: RESPIRE study design



- 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[2] (Figure 5)
- Time from randomization to discharge from hospital (TTHD) was the key secondary endpoint

Figure 5: Clinical severity status (primary endpoint, using a logistic regression analysis)

Assessed on a 7-point ordinal scale

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

ECMO, extracorporeal membrane oxygenation

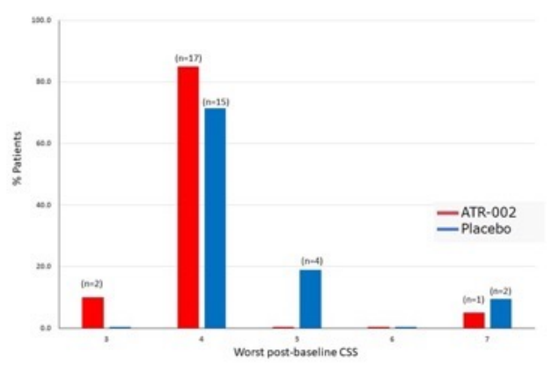
Safety

- Zapnometinib was safe and well tolerated, and the frequency of adverse events was low and similar between zapnometinib and placebo (Table 2). 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)

Table 1: Summary of safety

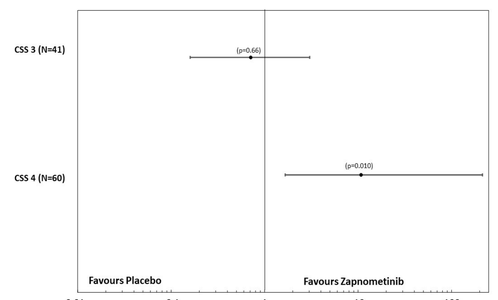
Number of patients with: n (%)	Zapnometinib (n = 51)	Placebo (n = 52)	Total (n = 103)
Any TEAEs	20 (39.2)	18 (34.6)	38 (36.9)
TEAEs occurring in >5% of either			
ALT increased	3 (5.9)	1 (1.9)	4 (3.9)
Diarrhea	4 (7.8)	3 (5.8)	7 (6.8)
Any severe TEAE	2 (3.9)	5 (9.6)	7 (6.8)
Severe TEAEs occurring in >5% 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)

Figure 6: Worst post-baseline CSS by treatment (CSS 4 subgroup, as treated)



Strong results were observed for the pre-planned endpoint of worst clinical status over the whole study duration. When analysing patients in baseline category CSS 4, we observed that in the three worst categories of CSS (stages 5-7), there was only one patient on zapnometinib but a total of 6 patients on placebo (all patients received standard of care). This finding in a small subgroup sample size (n=41) indicates a strong effect of zapnometinib in terms of preventing a further deterioration of hospitalized patients once treatment has started.

Figure 7: Forest Plot of Odds Ratios for Worst CSS by CSS subgroups (FAS, as-randomized)



In a logistic regression subgroup analysis, we observed an OR of 10,7 for patients in baseline subgroup CSS 4 (p-value = 0.0100), and an OR of 0.71 for patients in baseline subgroup CSS 3 (p-value =0.6445); p-value for interaction: 0.0414. This finding further confirms the strong effects for zapnometinib in the more severe group of patients (CSS 4 at baseline).

Summary of Results

The trial was terminated early in June 2022 as the success of global vaccination programs and prevalence of the Omicron variant 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.

Viral load reduction: Zapnometinib treatment led to a > 0.5. Log_{10} mean change from baseline over time in SARS-CoV-2 sputum samples from hospitalized COVID-19 patients on D8, D11, D15 and D30 **(Figure 1)**.

Increase of T cells: An 73.7% increase of T cells compared to baseline was found in zapnometinib treated patients compared to placebo treated patients **(Figure 2).**

Reduction of pro-inflammatory cytokines and chemokines: Zapnometinib treatment led to a reduction of most proinflammatory cytokines/chemokines, except IL-8/CXCL8 **(Figure 3)**.

Clinical Efficacy: In the as-treated analysis, the odds ratio for an improvement in clinical severity status (CSS) with zapnometinib versus placebo at Day 15 (primary endpoint) was 1.76 (95% CI 0.82 – 3.81; p=0.15). The strongest effect was seen in patients with more severe disease (CSS4) at baseline (OR=2.56 [95% CI 0.76 – 8.87; p=0.13]). Of the patients with baseline CSS4, only 1/20 (5%) zapnometinib-treated patients had a post-baseline worst CSS >4, compared with 6/21 (28.6%) placebo-treated patients indicating that zapnometinib has the capability to prevent further deterioration in patients, in terms of progression into more severe CSS (stages >4) **(Figure 6).**

In pre-planned subgroup analyses we could show that zapnometinib has the capability to prevent further deterioration in patients, in terms of progression into more severe CSS stages >4 (one patient on zapnometinib vs. 6 patients on placebo) **(Figure 6).**

Conclusions

- Zapnometinib did show strong trends for efficacy and was safe and well tolerated in hospitalized patients with COVID-19
- The trial had to be terminated prematurely due to difficulties recruiting severe patients. Still, consistent trends across several pre-planned efficacy endpoints, especially in patients with more severe disease at baseline (CSS 4), which were strongest in patients infected with non-Omicron SARS-CoV-2 variants, where observed.
- Zapnometinib reduced viral load, reduced pro-inflammatory cytokines/chemokines and supported an adaptive immune effector response
- Zapnometinib did show a strong effect in terms of preventing further disease progression in the group of more severe patients at baseline (CSS 4)
- Our data support proof-of-concept for the innovative approach of targeting the intracellular Raf/MEK/ERK signaling pathway in patients with severe viral respiratory infections
- Further development of zapnometinib is being planned in hospitalized patients with severe disease caused by influenza virus. The study protocol for this Phase 2 trial ("SURVIVE") is currently being finalized

References

1. Rohde et al. 2023 Efficacy and safety of zapnometinib in hospitalised adult patients with COVID-19: A randomised, double-blind, placebo-controlled, multi-centre, proof of concept / phase 2 trial (RESPIRE) *eClinMed* 2023 (accepted for publication)
2. World Health Organization. *WHO R&D Blueprint: Novel Coronavirus COVID-19 Therapeutic Trial Synopsis*.; :12.

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