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AvATher Group Meeting

AvATher Group Recommendations Following the Meeting with Atriva Therapeutics GmbH (Germany) on Zapnometinib (ATR-002)

18 September 2025

A. Context

As of January 2025, WHO surveillance data show that global influenza activity remains high, particularly across the Northern Hemisphere. Circulation of seasonal influenza A strains (A(H1N1)pdm09 and A(H3N2)) continues to rise in Europe, North America, and parts of Africa and Asia. In parallel, the ongoing avian influenza panzootic, with increasing evidence of cross-species transmission to mammals, raises concerns about the potential emergence of novel reassortant pandemic strains in humans.

Against this backdrop, the AvATher working group of ANRS - MIE has prioritized the identification and evaluation of promising antiviral candidates for influenza. Current treatment options, such as neuraminidase inhibitors (e.g., oseltamivir), RNA polymerase inhibitors (e.g., baloxavir), remain cornerstones of influenza therapy, but their effectiveness is limited by the risk of viral resistance and variable clinical efficacy, especially in severe cases. Similarly, the modest protection offered by existing influenza vaccines highlights the need for complementary therapeutic strategies.

Within this context, the AvATher group invited **Atriva Therapeutics GmbH (Germany)** to present their candidate **zapnometinib (ATR-002),** a host-directed antiviral currently in clinical development. Its novel mechanism of action targeting the Raf/MEK/ERK signalling pathway, combined with evidence of antiviral and immunomodulatory activity, positions zapnometinib as a promising option for further evaluation, particularly in the setting of severe influenza.

B. Zapnometinib (ATR-002): Summary of mechanism of action and key characteristics[1-2]

ATR-002 is an inhibitor of the kinase isoforms MEK1 and MEK2. It is derived from the MEK inhibitor CI-1040, a small-molecule that inhibits the dual-specific kinases MEK1 and MEK2. The drug was originally developed by Pfizer about 25 years ago. ATR-002 was designed by

[1] Schreiber A, Viemann D, Schöning J, Schloer S, Mecate Zambrano A, Brunotte L, Faist A, Schöfbänker M, Hrincius E, Hoffmann H, Hoffmann M, Pöhlmann S, Rescher U, Planz O, Ludwig S. The MEK1/2-inhibitor ATR-002 efficiently blocks SARS-CoV-2 propagation and alleviates pro-inflammatory cytokine/chemokine responses. Cell Mol Life Sci. 2022 Jan 10;79(1):65. doi: 10.1007/s00018-021-04085-1.

[2] Laure M, Hamza H, Koch-Heier J, Quernheim M, Müller C, Schreiber A, Müller G, Pleschka S, Ludwig S, Planz O. Antiviral efficacy against influenza virus and pharmacokinetic analysis of a novel MEK-inhibitor, ATR-002, in cell culture and in the mouse model. Antiviral Res. 2020 Jun;178:104806. doi: 10.1016/j.antiviral.2020.

exploiting the fact that many viruses hijack the Raf/MEK/ERK signalling pathway to ensure their replication.

In influenza virus infection, this pathway is activated in two phases, with the late stage being functionally most relevant, as it drives the nuclear export of viral genome-containing ribonucleoprotein complexes (vRNPs) into the cytoplasm. Inhibition of this pathway with MEK1/2-specific inhibitors prevents this export. This results in nuclear retention of vRNPs, impaired viral propagation, and overall antiviral activity.

In SARS-CoV-2, which does not require a nuclear phase for replication, ATR-002 inhibits the transfer of viral material to the ER/Golgi apparatus, thereby impairing viral assembly (unpublished and non peer-review results).

The Raf/MEK/ERK signalling pathway is also involved in immune regulation. Its inhibition therefore not only interferes with viral replication but also helps restore immune balance. This results in a dual effect: (1) a direct antiviral effect through inhibition of viral propagation by targeting host-cell kinases, and (2) an immunomodulatory effect by dampening pathological processes of the innate and adaptive immune responses. Targeting host-cell pathways further reduces the risk of viral resistance and supports broad applicability. In addition, early safety and pharmacokinetic data support favourable clinical translation.

C. Preclinical Assessment of Zapnometinib (ATR-002)

I. Influenza

- **In vitro antiviral activity[2]**

ATR-002 reduced viral titres of both pandemic H1N1pdm09 and seasonal H3N2 strains in a dose-dependent manner. At **10 µM**, viral titres decreased by ~50% for H1N1pdm09 and ~87% for H3N2, while 1 µM was ineffective. Compared with CI-1040, an almost **10-fold higher concentration of ATR-002** was required to achieve a similar reduction. EC50 values ranged between **4.2–6.4 µM** across H1N1pdm09, H3N2, and influenza B/Lee/40, with CC50 values of **271.8 µM (A549)** and **188.6 µM (MDCK II)**, resulting in selectivity indices of 42.8, 60.4, and 45.0, respectively. On the molecular level, ATR-002 blocked the nuclear export of viral vRNPs, causing their retention in the nucleus.

In addition to the pandemic H1N1pdm09 and seasonal H3N2 strains, Zapnometinib has been tested against a broad panel of influenza viruses. For influenza A, these included H1N1 strains (including oseltamivir- and baloxavir-resistant variants), H3N2 strains (including baloxavir-resistant variants), as well as avian H5N1 and H7N9 viruses. For influenza B, efficacy was demonstrated against B/Lee, B/Münster/341-200/18, and B/Münster/356-200/18.

- **Pharmacokinetics and bioavailability (mice)**

Pharmacokinetic studies in NMRI mice demonstrated that ATR-002 achieved markedly higher plasma exposure than CI-1040 after both i.v. (AUC 860 vs 223 µg*h/ml) and oral administration (AUC 1954 vs 156 µg*h/ml). Unlike CI-1040, ATR-002 remained

detectable after oral dosing throughout the observation period, indicating improved bioavailability.

- **In vivo efficacy (lethal H1N1pdm09 mouse model)[2]**

C57BL/6 mice were infected with a lethal dose of H1N1pdm09 and treated orally with **ATR-002 (8.4–75 mg/kg/day, TID)** or **CI-1040 (25–450 mg/kg/day, TID)**. Lung virus titres were measured 24 h after infection. ATR-002 significantly reduced lung viral titres at lower doses than CI-1040. While CI-1040 required 450 mg/kg/day to achieve a measurable effect, ATR-002 was effective at 25 and 75 mg/kg/day.

In survival studies, mice received oral ATR-002 at 50 mg/kg/day starting 24, 48, or 72 h post-infection. **Survival rates were 75% (6/8) at 24 h, 37.5% (3/8) at 48 h, and 25% (2/8) at 72 h**, all statistically significant compared to controls. Surviving animals lost weight initially and developed mild to moderate symptoms but recovered fully by day 14, with complete resolution of disease and regained body weight. ATR-002 was well tolerated in uninfected mice, causing only minor transient weight loss (<5%).

II. SARS-Cov-2

- **In vitro antiviral activity[3]**

  Zapnometinib inhibited the propagation of SARS-CoV-2 omicron and other **alpha** pathogenic human coronaviruses (HCoV-OC43, HCoV-229E, SARS-CoV-1) in Virospot and virus yield reduction assays. EC_{50} values ranged from **16.1 µM (HCoV-OC43)** to **37.9 µM (SARS-CoV-2 omicron)**, with no cytotoxicity observed. These findings extend prior results showing efficacy against SARS-CoV-2 alpha, beta, and delta variants, supporting its broad antiviral potential and resilience against emerging variants[4].

- **Pharmacokinetics of zapnometinib in hamsters[3]**

  The pharmacokinetics of zapnometinib were assessed in Syrian hamsters to determine dosing for in vivo efficacy studies and to evaluate tolerability. Animals received single oral doses of 15, 30, or 60 mg/kg, and blood samples were collected up to 24 hours post-administration. Serum concentration–time curves showed a monophasic profile with dose-proportional increases in exposure. The time to peak concentration (Tmax) was 2 hours at 15 and 30 mg/kg and 4 hours at 60 mg/kg, while the half-life was consistent across groups at 2–3 hours. At the highest dose, plasma levels at 24 hours reached 5.32 µg/mL (13 µM), below the 10 µg/mL (24.4 µM) required for 50% MEK inhibition. All doses were well tolerated without adverse

[3] Füll Yvonne , Schüssele Lara M. , Hamza Hazem , Hoffmann Helen , Bauer Martin , Stenglein Stephan , Pötz Oliver , Steinhilber Andreas , Anselm Viktoria , Delany Mark W. , Van den Brand Judith M. A. , Van Amerongen Geert , De Waal Leon , Pleschka Stephan , Ludwig Stephan , Planz Oliver. Antiviral and immunomodulatory effect of zapnometinib in animal models and hospitalized COVID-19 patients. Front. Immunol., 22 September 2025, Sec. Viral Immunology, Volume 16 - 2025, https://doi.org/10.3389/fimmu.2025.1631721

[4] Schreiber A, Viemann D, Schöning J, Schloer S, Mecate Zambrano A, Brunotte L, Faist A, Schöfbänker M, Hrincius E, Hoffmann H, Hoffmann M, Pöhlmann S, Rescher U, Planz O, Ludwig S. The MEK1/2-inhibitor ATR-002 efficiently blocks SARS-CoV-2 propagation and alleviates pro-inflammatory cytokine/chemokine responses. Cell Mol Life Sci. 2022 Jan 10;79(1):65. doi: 10.1007/s00018-021-04085-1.

events. Based on these results, a regimen of 100 mg/kg loading dose followed by 75 mg/kg daily was chosen for efficacy testing, corresponding to the human Phase 2 dosing scheme and ensuring sustained serum concentrations above the MEK inhibition threshold. Pulmonary exposure in hamsters has not been explored.

- **In vivo efficacy of zapnometinib in SARS-CoV-2–infected hamsters**[3]
  An in vivo study in SARS-CoV-2–infected Syrian hamsters assessed the efficacy of zapnometinib given orally at a **100 mg/kg** loading dose followed by **75 mg/kg daily**, starting either **+4 h or +24 h** post-infection. Treatment was well tolerated and led to significant reductions in viral titres in throat swabs and nasal turbinates, particularly with early initiation, while later treatment provided greater improvements in lung pathology. Histopathology confirmed reduced inflammation, oedema, haemorrhage, and pneumocyte hyperplasia in treated animals. Overall, zapnometinib showed antiviral activity and protective effects in the hamster model, with the timing of treatment influencing outcomes.

Conclusion: While zapnometinib shows encouraging efficacy, certain limitations of host-targeted antivirals must be considered. In antiviral drug development, **IC_{50} and CC_{50} values are often used as gold-standard benchmarks**; however, these parameters are not fully comparable across drug classes. **Direct-acting antivirals** typically achieve nanomolar **IC_{50}** values by targeting viral proteins, resulting in high selectivity indices. By contrast, **host-targeted drugs** like zapnometinib act on cellular pathways, where effective concentrations are usually in the micromolar range. This difference does not imply lower therapeutic potential but instead reflects a **fundamentally distinct mechanism of action**. Thus, IC_{50} and CC_{50} values should not be the sole determinants of the compound's strength, as host-targeted approaches may provide **unique advantages in resistance management and broad-spectrum activity**, offering a complementary strategy to direct-acting antivirals. To date, preclinical data demonstrate that Zapnometinib exhibits antiviral efficacy not only against influenza A and B viruses, but also against a range of other pathogens including Hantavirus, RSV, hMPV, SARS-CoV-2, SARS-CoV-1, MERS-CoV, Dengue virus types 1–4, West Nile virus, Zika virus, and Yellow Fever virus.

D. Immune Response Modulation in Experimental Models

Beyond its direct antiviral effects, zapnometinib also modulates the host immune response. It acts on two levels: cytokine/chemokine regulation and cellular antiviral immunity. In severe influenza and COVID-19, excessive production of pro-inflammatory cytokines such as IL-6, TNF-α, and CXCL10 can drive harmful cytokine storm–like responses. Zapnometinib reduces these pro-inflammatory mediators without completely abolishing them, thereby mitigating excessive inflammation while preserving essential antiviral activity. In parallel, it restores immune balance by shifting responses toward a more controlled Th1/Th2 profile and limiting immunopathology. On the cellular side, zapnometinib enhances naïve and central memory T-cell populations, preserves effector T-cell activity needed for viral clearance, and promotes a shift away from exhausted or terminally differentiated T cells,

ultimately supporting long-term immune competence and a more resilient immune landscape.

ATR-002 was tested for its impact on virus-induced cytokine and chemokine responses in SARS-CoV-2 infection models and in polyI:C-stimulated cells. In infected Calu-3 and A549-ACE2/TMPRSS2 cells, treatment with ATR-002 (100–150 µM) led to a marked reduction in pro-inflammatory cytokine/chemokine expression, including IL-6, CXCL8, CXCL10, CCL2, and CCL5, with the strongest effects on CXCL8 (~89% reduction) and CXCL10, and weaker effects on IL-6 and CCL5 (~45–50% reduction). Importantly, interferon-mediated antiviral genes (IFNβ, MxA) were not affected, showing that the drug selectively reduced inflammatory mediators[1].

Similar results were obtained in virus-free systems using polyI:C stimulation, where ATR-002 significantly reduced cytokine/chemokine mRNA and secretion without altering the IFN response. These findings indicate that ATR-002 can attenuate the cytokine storm associated with severe COVID-19, by lowering pro-inflammatory signalling while preserving antiviral defence mechanisms[1].

In the SARS-CoV-2 hamster model, cytokine and chemokine levels rose only marginally, limiting its use for immunomodulatory assessment. In contrast, in an **LPS-induced acute lung injury mouse model**, zapnometinib (25 mg/kg) broadly downregulated inflammatory genes (**IL-1β, IL-6, Ccl2, Cxcl1, Cxcl10, Ccl3**) while leaving **IFN-α (Ifna2)** unaffected, indicating preserved antiviral responses. Similarly, in **human PBMCs** stimulated with LPS, zapnometinib significantly reduced **IL-1β, IL-6, IL-8, IP-10, MCP-1, MIP-1α, and TNF-α**. These results provide the first in vivo confirmation of zapnometinib's direct anti-inflammatory effect, selectively reducing pro-inflammatory mediators while leaving IFN-α expression unaffected[3].

E. Clinical Development of Zapnometinib (ATR-002)

To date, two Phase I trials (one in influenza, one in COVID-19) and one Phase II trial (COVID-19) have been completed.

- **Influenza (Phase I):** A single- and multiple-dose escalation study in healthy volunteers evaluated the safety (treatment-emergent adverse events), tolerability, and pharmacokinetics (AUC_0–t, Cmax, Tmax, t½) of ATR-002 given for seven days[5].
- **COVID-19 (Phase II – RESPIRE):** A trial in hospitalized adult patients assessed the safety and efficacy of ATR-002, focusing on the resolution of clinical symptoms[6].
- **COVID-19 (Phase I):** A dose-escalation study in healthy volunteers investigated safety and tolerability versus placebo, alongside pharmacokinetics, pharmacodynamics (target engagement), and potential food–drug and drug–drug interactions (FDI/DDI)[7].

[5] https://clinicaltrials.gov/study/NCT04385420?intr=ATR-002&rank=1
[6] https://clinicaltrials.gov/study/NCT04776044?intr=ATR-002&rank=2
[7] https://clinicaltrials.gov/study/NCT05555823?intr=ATR-002&rank=3

Clinical efficacy of zapnometinib (RESPIRE, COVID-19, Phase II)[8]

Zapnometinib showed a non-significant trend toward improved clinical status compared with placebo at Day 15 across primary, as-treated, and per-protocol analyses (p=0.15 and p =0.35). Subgroup analyses suggested greater benefit in patients with more severe disease (clinical severity status [CSS] 4; p=0.13) and in those infected with non-Omicron variants (p=0.10).

For hospital discharge, zapnometinib shortened median stay by ~1.5 days in CSS 4 patients (8.5 vs 10.0 days), though the difference was not statistically significant (p=0.25). Overall population effects were smaller (p=0.27) compared to placebo. Other secondary endpoints generally supported a trend for greater benefit in patients with severe disease.

Safety and tolerability (RESPIRE, COVID-19, Phase II)[8]

Adverse event (AE) frequency was low and comparable between treatment arms. The most common treatment-emergent AEs were mild increases in alanine aminotransferase and diarrhea, both occurring at low rates. Most AEs were mild or moderate; severe events occurred in 6.8% of patients overall, more often in the placebo group (9.6%) than in the zapnometinib (3.9%) group. Severe dyspnea was the only severe AE reported in >5% of patients, and it occurred only in the placebo arm. No serious AEs were reported in >5% of patients. Three deaths occurred (two placebo, one zapnometinib), all before Day 30 and all deemed unrelated to treatment.

Antiviral effect of zapnometinib in the clinical trial[3]

In hospitalized COVID-19 patients, viral load was monitored by RT-qPCR in sputum and nasopharyngeal samples up to Day 30. Zapnometinib was associated with greater reductions in mean viral load compared with placebo, particularly in sputum samples from Day 8 onward. In patients infected with non-Omicron variants, zapnometinib produced a significant reduction of +1.57 $\log_{10}$ copies/ml on Day 8 (p=0.010), with reductions of >1 $\log_{10}$ maintained through Days 11–30 (p=0.055–0.067). Nasopharyngeal samples also showed reductions in viral load, though less pronounced.

These findings confirm that zapnometinib exerts both immunomodulatory and antiviral effects in patients with severe SARS-CoV-2 infection.

Effect on cytokines and chemokines in the clinical trial[3]

In the RESPIRE Phase II study (CSS 3–4 COVID-19 patients), multiplex ELISA of serum samples collected up to Day 30 showed that zapnometinib significantly reduced **MCP-1, MIP-1α, and IFN-γ (all p<0.0001)**, as well as **IL-6 (p=0.0017)**, compared with placebo.

[8] Rohde G, Stenglein S, Prozesky H, Manudhane G, Sandulescu O, Bauer M, Overend T, Koch W, Neuschwander D, Planz O, Torres A, Witzenrath M. Efficacy and safety of zapnometinib in hospitalised adult patients with COVID-19 (RESPIRE): a randomised, double-blind, placebo-controlled, multicentre, proof-of-concept, phase 2 trial. EClinicalMedicine. 2023 Oct 4;65:102237. doi: 10.1016/j.eclinm.2023.102237.

No changes were observed for TNF-α, and IL-8/CXCL8 showed a slight, non-significant increase. These findings support the preclinical data demonstrating zapnometinib's capacity to reduce pro-inflammatory cytokine and chemokine expression.

Modulation of adaptive immune response in the clinical trial[3]

Zapnometinib treatment increased circulating immune cells compared with placebo. Over 30 days, lymphocyte counts rose by **44.5%**, with a more pronounced increase in **T cells (+73.7%, p=0.040)** and **plasma B cells (+61.8%)**. In contrast, **memory B cells decreased (-37.4%, p=0.037)**. These effects were consistent across observation days, indicating that zapnometinib exerts a positive immunomodulatory effect on both innate and adaptive immune responses.

Conclusion

Clinical studies have shown that zapnometinib is generally safe and well tolerated, with a favorable safety profile and encouraging signals of efficacy, including reduced viral load, particularly in patients with more severe COVID-19. Before clinical trials, zapnometinib was thought to act mainly through its antiviral effect. However, results from the RESPIRE trial suggest that its immunomodulatory activity plays an even stronger role, while antiviral activity is still maintained. This shift highlights that zapnometinib balances antiviral defense with modulation of excessive inflammation, broadening its potential for both viral and non-viral indications.

F. Discussion

Q1: I agree that for host-directed antivirals, IC_{50} and EC_{50} values from in-vitro studies are more difficult to interpret than for direct-acting antivirals. In your influenza animal models, what is the maximum absolute viral load reduction you observe, expressed in quantitative terms rather than relative percentages? For example, are you able to exceed a 1-log decrease, reaching 2 or even 3 logs?

As demonstrated in the Laure et al. (2020)[2] paper, we achieved a viral load reduction of about 1.5 to 2 logs. In the hamster study with SARS-CoV-2, the effect was smaller, around 1 log reduction.

A similar phenomenon was observed with molnupiravir: in cell culture, the CC_{50} appeared excellent compared to zapnometinib, and in animal experiments, viral load reductions were comparable between molnupiravir and zapnometinib. However, in hospitalized patients, molnupiravir did not reduce viral load, whereas zapnometinib did show reductions in the RESPIRE trial.

This strengthens our confidence in the translational relevance of zapnometinib, particularly since we have already demonstrated stronger MEK inhibition effects in influenza compared to SARS-CoV-2, although we do not yet have patient data in severe hospitalized cases to confirm success in influenza.

Q2: I fully agree that the described mechanism of action against influenza is strong and well demonstrated. Given that the viral load reduction observed in preclinical influenza models was not very strong, have you considered evaluating zapnometinib in combination with other influenza antivirals to potentially enhance its activity and reduce the risk of resistance emerging?

This is an excellent point, and in fact we have already tested this in preclinical models. We evaluated zapnometinib in different combinations, first with Tamiflu and then with baloxavir, to determine whether these combinations would interfere with efficacy. Based on the results, I would personally recommend combining with Tamiflu rather than baloxavir.

It's important to note that neither Tamiflu nor baloxavir shows efficacy in severe influenza patients, but both can strongly reduce viral load in the early phase of infection. Adding zapnometinib could then inhibit viral particles that spread systemically. This is the strategy I would recommend.

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Q3: I have a question regarding the immune responses you evaluated in both the in-vivo and in-vitro context. Did you investigate the innate immune pathways, such as type I and type III interferons, for example IFN-α, IFN-β, and IFN-λ?

We investigated this and reported it in the Schreiber et al. (2020)[1] paper. We found that zapnometinib does not interfere with type I interferon signaling and, importantly, does not affect MxA expression. Thus, the antiviral innate immune response remains intact. This is because the pathway is regulated by interferon regulatory factors 3 and 7 (IRF3/IRF7), which are not influenced by the Raf/MEK/ERK signaling pathway targeted by zapnometinib.

Q4: In the mouse model of acute lung injury, you showed a decrease in pro-inflammatory cytokines. However, I understood that IL-1β and TNF-α are not modulated by your drug. Could this be related to NF-κB activity, or what is your explanation?

In this development program, we have also encountered data that does not always fit together perfectly, as you mentioned. In the animal model, we know that NF-κB signaling pathway is very strong. In the past, we also tested NF-κB inhibitors with this drug and saw a much stronger effect on cytokine and chemokine responses. It is not always possible to get 100% alignment when moving from cell culture to animal models, but both are important steps before testing in humans.

That said, in humans we do observe reductions in TNF-α and interferon-γ. We acknowledge that TNF-α is a crucial factor, and further investigation is needed to better understand how zapnometinib influences TNF-α specifically, including studies focusing on this cytokine alone.

Q5: You show us less exhaustion of naïve T-cells, but not the effector cells. I know from the HIV-field, usually, we look for the exhaustion of effector cells rather than naïve-T cells. Is that correct?

That is correct, and I apologize for not showing the effector cell data. The reason is that these results are brand new and still unpublished. We already have complete datasets for all the cell populations. Since we observed effects on naïve and central memory cells, we then extended our analyses to effector cells, using data from the RESPIRE trial. However, given the large number of sub-populations, the effector cell results have not yet been presented.

Q6: I have a question on the pharmacokinetic data of this compound. I understand that the half-life is quite long in humans compared to animals, around 19 hours. Is that correct? That would mean steady state is achieved after about 5–7 days, making rapid onset of action difficult except at low concentrations?

We measured this over 96 hours. The half-life in humans is dose-dependent, ranging from about 22 to 30 hours. You are correct that steady state is achieved after approximately 5 days.

Q7: In your phase 1 study, plasma concentrations of the drug were around 1–2 µM. Is that accurate?

It depends on the dosing regimen, as reported in the Rhode et al (2023)[8] paper. We started with a 900 mg loading dose followed by 600 mg. I apologize for not showing the phase 2 data yet, we tested 1500, 1200, 900, and 600 mg doses, and the manuscript is in preparation. We have evidence that the compound is safe at 900 mg and also at 1200 mg. From an immunological perspective, I would recommend 1200 mg.

Q8: What about the metabolism of this drug? Is it metabolized through cytochrome P450 enzymes, for example CYP3A4, as it is common for kinase inhibitors? If so, could this lead to variability in exposure between patients? And could you share the range of variability you observed in plasma concentrations during the phase 2?

Yes, I can confirm the drug is metabolized through CYP3A4. I do not have the exact data at hand, but the variability was, to my knowledge, less than 10-fold between patients.

Q9: You mentioned the safety of your product rather briefly. What preliminary data do you have on the safety profile from animal models for this compound?

We conducted safety and toxicology studies in both rat and dog models, and these results have also been published. The favorable findings from these studies supported the initiation of two phase I studies and the subsequent phase II trials. In animal models, as in humans, the compound was well tolerated and showed a good safety profile.

Q10: What about your clinical development plan? You have carried out phase II studies in COVID-19 but not in influenza. What are the next steps in your clinical

development program? Have you planned to move to a phase III trial in COVID-19, or in influenza infections?

Our expertise is in influenza, and the full development program was originally focused on hospitalized influenza patients. During the COVID-19 pandemic, we shifted our efforts to develop clinical trials in COVID-19, as many others did. Afterward, our plan has been to continue with a phase II trial in hospitalized influenza patients. Everything is prepared, but funding remains the missing piece. We have a complete plan to conduct a trial in influenza. At this stage, we do not believe it makes sense to continue with COVID-19 because our strategy relies entirely on hospitalized patients, and zapnometinib is not intended for uncomplicated infections.

Q11: Concerning your development plan for the phase II trial in influenza, do you think it would be possible to carry it out in France, with the support of ANRS – MIE, provided that funding is available?

Yes, we would very much welcome such an opportunity.

G. Overall Assessment and AvAThER Group Recommendations

In contrast to COVID-19, the situation in influenza is more straightforward. The mechanism of action is well defined and supported by robust experimental evidence, with antiviral activity demonstrated in vivo in preclinical models. While the magnitude of the effect observed to date appears modest, especially when compared with molnupiravir, which shows stronger efficacy in preclinical models, **zapnometinib remains of clear scientific interest**.

Points to consider include its **relatively long half-life of approximately 19 hours** (requiring 5 days to reach steady state and thus potentially delaying onset of clinical effect in influenza patients), its metabolism via cytochrome CYP3A4 (introducing variability between subjects), and its relatively **high EC_{50} values in the supra-micromolar range** (with residual plasma concentrations of 2-3 µM).

In conclusion, the group feels that zapnometinib could be further explored in combination therapies, as its host-directed mechanism of action may offer complementarity with direct-acting antivirals and contribute to resistance management.

Overall Assessment of Zapnometinib

Pre-exposure Prophylaxis	Post-Exposure Prophylaxis	Out-patient Treatment	In-patient Treatment
X	X	X	**To follow***

*** = in combination therapies.**

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