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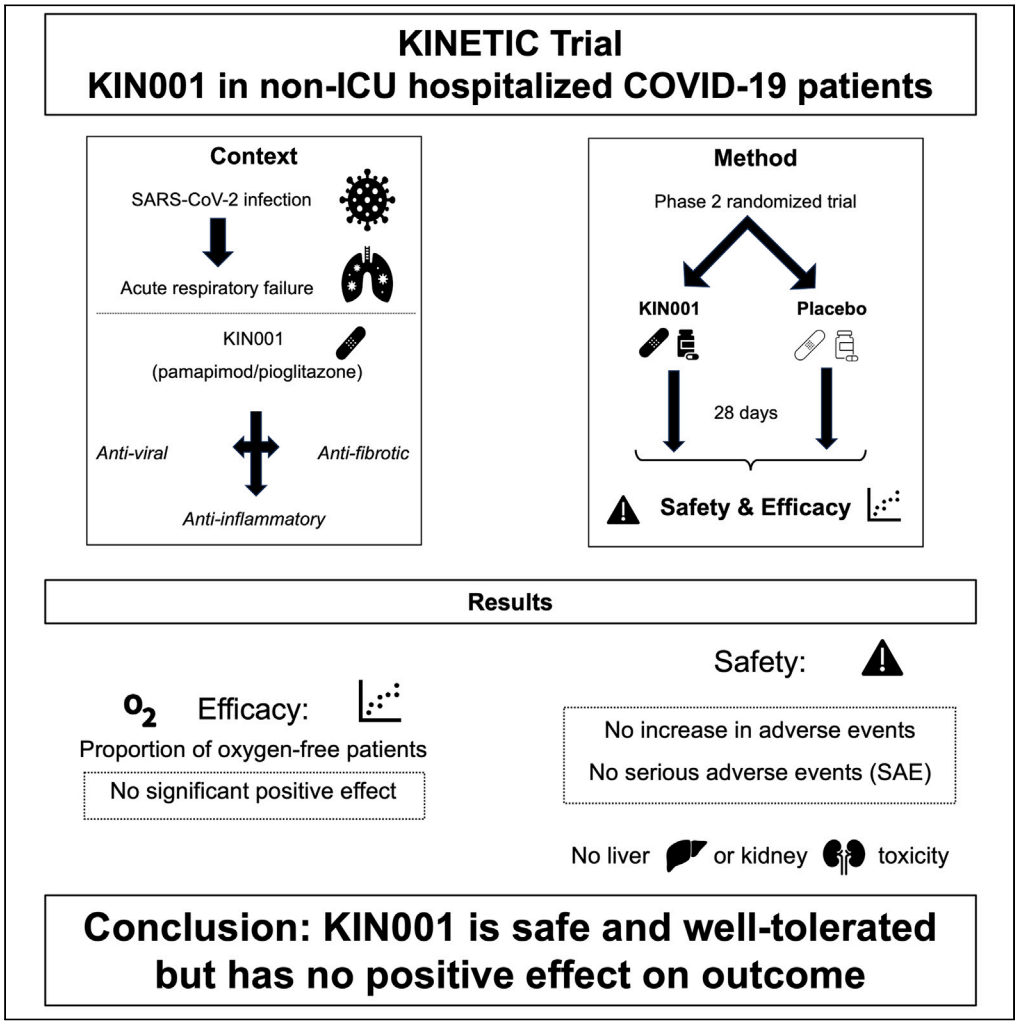

Thierry Fumeaux, Claudia Berger, Alexander Bausch, Matthew Wright, Urosh Vilimanovich, Ivan Soldatovic, Maria J.G.T. Vehreschild

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Highlights

KIN001 (pamapimod-pioglitazone combination) is active against SARS-CoV-2 *in vitro*

KIN001 is anti-inflammatory and anti-fibrotic and may thus improve COVID-19 outcome

KINETIC is a randomized controlled phase 2 trial in hospitalized COVID-19 patients

KIN001 was safe and well-tolerated but had no effect on the primary endpoint

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The KINETIC phase 2 randomized controlled trial of oral pamapimod-pioglitazone in non-critically ill COVID-19 inpatients

Thierry Fumeaux,[1,4,*] Claudia Berger,[1] Alexander Bausch,[1] Matthew Wright,[1] Urosh Vilimanovich,[2] Ivan Soldatovic,[2] and Maria J.G.T. Vehreschild[3]

SUMMARY

The combination of pamapimod and pioglitazone (KIN001) has a synergetic antiviral, anti-inflammatory, and antifibrotic activity, which may prevent evolution toward COVID-19-associated severe respiratory failure. In a randomized, placebo-controlled, double-blind, phase 2, multicenter trial, 128 non-critically ill hospitalized patients with confirmed COVID-19 were treated with KIN001 or a placebo for 28 days. The proportion of patients alive and free of oxygen or respiratory support at the end of the therapy was lower than anticipated but not different in the two groups (KIN001 n = 19, 29%, placebo n = 21, 33%). 85 participants had at least one adverse event, with no difference in the number and distribution of events between the two groups. The clinical trial was stopped for futility, mainly due to a lower-than-expected incidence of the primary endpoint. KIN001 was safe and well-tolerated but had no significant effect on clinical outcome.

INTRODUCTION

The COVID-19 caused by SARS-CoV-2 was declared a pandemic in March 2020 and has caused over 750 million cases worldwide: while most patients have mild illness; however, those with comorbidities and with more severe illness often require hospitalization, with a significant associated morbidity and mortality. With the emergence of new variants and the progresses in management, the global severity of COVID-19 has decreased, but many patients still progress to acute respiratory failure (ARF) and require an advanced respiratory support in the form of oxygen therapy, high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (MV), or extracorporeal membrane oxygenation (ECMO), and are at higher risk of death.[1,2] To date, few therapies have proven beneficial to reduce the risk of ARF and dexamethasone and the antiviral remdesivir are the only currently recommended drugs, while JAK inhibitors and anti-IL-6 reserved to selected cases.[3] New therapies are needed to decrease the risk of ARF in hospitalized non-critically ill patients, and drug repurposing is an interesting approach in this respect.

Pamapimod is a selective inhibitor of p38 mitogen-activated protein kinase-alpha (p38 MAPKα) that was developed as an anti-inflammatory drug for rheumatoid arthritis.[4,5] The p38 MAPKs mediate the cellular response to stress, infection, and pro-inflammatory factors.[6] SARS-CoV-2 infection upregulates the p38 MAPK pathway, and the inhibition of this pathway has been shown to decrease viral replication *in vitro* and to reduce the expression of IL-6, CXCL8, CCL20, and CCL2.[7] The anti-diabetic drug pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist. Diabetes is a risk factor for poor outcomes in COVID-19 and the use of pioglitazone in diabetic COVID-19 patients may be associated with a decreased risk of hospital admissions.[8,9] The combination of pamapimod and pioglitazone, called KIN001, reduces the *in vitro* replication of all major SARS-CoV-2 variants, and its anti-inflammatory and antifibrotic properties support its clinical evaluation in COVID-19.[10]

KINETIC (KIN001 to decrease the risk of endotracheal intubation in COVID-19) was a phase two randomized and controlled trial to study the effect of KIN001 on the risk of severe ARF and death in non-critically ill hospitalized patients. We report the results of a planned interim analysis that led to early termination of the trial.

RESULTS

Study process

The first patient was randomized on April 8, 2021. As of June 1, 2022, 132 patients (intention-to-treat population) had been randomized to KIN001 (n = 68) or placebo (n = 64): 128 patients (modified intention-to-treat population [mITT]) had completed the 4-week observation

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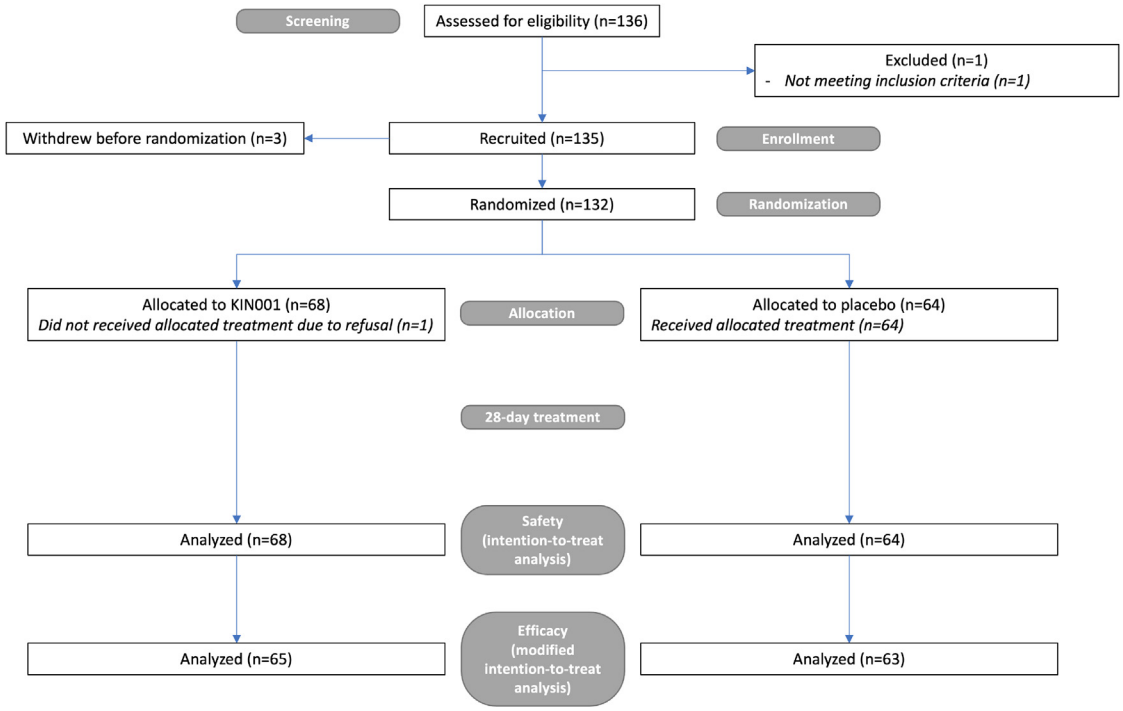

Figure 1. KINETIC study CONSORT flow diagram

period and were included in the efficacy analysis (Figure 1). In the mITT population, the conditional power calculation revealed a low probability (19.4%) to achieve a significant positive effect of KIN001, below the 20% threshold corresponding to the futility boundary of the 80% minimal power. Based on these data, as suggested by the DSMB, the Sponsor decided to stop the trial and the database was closed. We present here the efficacy data obtained in the 128 patients included in the interim analysis, and the safety and laboratory data for the 132 patients who completed the study.

Patients characteristics

The characteristics of patients at baseline were similar across the KIN001 and placebo groups (Table 1). The mean age was 67 years (SD ± 11), with 54% females and 46% males. 127 participants had a WHO Clinical Progression Scale score of four or five, four patients a value of six, and the value was missing for one.[11] The overall median time from symptom onset to randomization was 9 · 0 days in the placebo arm (IQR 7·0–11·0) and 8 · 0 days in the KIN001 arm (IQR 6·0–13·0) (Table 1).

According to local practices, the patients were treated with anti-viral drugs (favipiravir, umifenovir, remdesivir, riamilovir), corticosteroids (dexamethasone, prednisone, and methylprednisolone), immunomodulating drugs (tocilizumab, levilimab, baricitinib, tofacinib), and antibiotic therapies (Table 1). The majority of patients (82 · 6%) were treated with steroids, in line with the available evidence. In a large proportion of patients, the steroids were associated with an anti-viral drug and/or an immunomodulating drugs.

Primary and secondary outcome results

In the mITT population, the proportion of patients who were alive and without oxygen or respiratory support during the 28-day treatment period was not significantly different between the KIN001 and control groups (29 · 2% vs. 33 · 3%, p = 0 · 617) (Table 2). The proportion of patients who died or required invasive MV, the original primary endpoint, did not differ significantly (6 · 3% for control vs. 12 · 6% for KIN001, 0 · 204), and the distribution of the most advanced supportive respiratory treatment during the observation period was not significantly different between the two groups (Table 2). The number of days alive and free of any oxygen or ventilatory support therapy was not different between the groups (Table 2). There was no difference in changes in CRP or white blood cell count between the treatment arms during the 28-day observation period (Table 3).

Safety and adverse events

Safety and tolerability were analyzed in the intention-to-treat population of patients who were randomized at the time of the interim analysis (n = 132). Overall, 85 patients (64%) presented with an adverse event during the 28-day observation period, with no significant difference between groups in the incidence and distribution of events (Table 4). There were no deaths in the placebo group and three deaths in the KIN001

Table 1. Patient characteristics in the intention-to-treat population

	KIN001 (n= 68)	Placebo (n=64)	Total (n=132)
Age (year), mean (SD)	66 (12)	68 (10)	67 (11)
Weight (kg), mean (SD)	88 (23)	87 (21)	88 (22)
BMI[a] (kg/m^2), mean (SD)	31·1 (6·6)	29.8 (7·9)	30.6 (7·3)
Female sex, n (%)	34 (50)	37 (58)	71 (54)
Duration of symptoms (days), median (IQR[b])	8·0 (6·0–13·0)	9·0 (7·0–11·0)	8·6 (6·2–12·4)
WHO category at inclusion, n (%)[c]			
4	23 (33·8)	24 (37·5)	47 (35·9)
5	41 (60·3)	39 (60·9)	80 (61·1)
6	3 (4·4)	1 (1·6)	4 (3·1)
Vitals signs and laboratory value at inclusion, mean (SD)			
Heart rate (beats/minute)	80 (13)	80 (11)	80 (12)
Respiratory rate (breaths/min)	21 (3)	20 (2)	21 (3)
Systolic blood pressure (mmHg)	131 (16)	130 (17)	131 (17)
Diastolic blood pressure (mmHg)	77 (9)	77 (11)	77 (10)
SpO2[d] (%)	95 (3)	96 (2)	95 (2)
PaO2[e] (mmHg)	71 (13)	77 (18)	74 (16)
FIO2[f] (%)	36 (19)	30 (9)	34 (15)
CRP[g] (mg/l), median (IQR)	35 (15–73)	38 (16–77)	36 (15–77)
White blood cells count (10^9/l), median (IQR)	6·6 (4·5–8·6)	5·8 (4·0–7·6)	6·1 (4·2–7·8)
Co-morbidities and chronic conditions[h], n (%)			
Hypertension	58 (85·3)	53 (82·8)	111 (84·1)
Obesity	20 (29·4)	17 (26·6)	37 (28·0)
Diabetes mellitus type 2	15 (22·1)	14 (21·9)	29 (22·0)
COPD/asthma	17 (25·0)	10 (15·6)	27 (20·5)
Atrial fibrillation	11 (8·3)	10 (15·6)	21 (15·9)
Ischemic heart/coronary artery disease	19 (27·9)	16 (25·0)	35 (26·5)
Cerebrovascular disease/stroke	8 (11·8)	10 (15·6)	18 (13·6)
Cancer	5 (7·4)	9 (14·1)	14 (10·6)
Co-administered therapies, n (%)			
Anti-viral therapy	38 (55·9)	42 (65·6)	80 (60·6)
Corticosteroid therapy	55 (80·9)	54 (84·4)	109 (82·6)
Anti-IL-6[i] monoclonal antibody therapy	23 (33·8)	21 (32·8)	44 (33·3)
JAK[j] inhibitor therapy	8 (11·8)	15 (23·4)	23 (17·4)
Antibiotic therapy	45 (66·2)	30 (46·9)	75 (56·8)
Anti-viral and corticosteroid combination	31 (45·6)	35 (54·7)	66 (50·0)
Anti-viral, corticosteroids and IL-6/JAK combination	25 (36·8)	26 (40·7)	51 (38·6)

[a]BMI: body mass index.
[b]IQR: interquartile range.
[c]One value is missing for a patient randomized to KIN001.
[d]SpO2: saturation of peripheral oxygen.
[e]PaO2: arterial partial pressure of oxygen.
[f]FIO2: fraction of inspired oxygen.
[g]CRP: C-reactive Protein.
[h]total numbers and percentage exceed the total, due to the co-existence of several conditions in several patients.
[i]IL-6: interleukin-6.
[j]JAK: Janus kinase.

Table 2. Primary and secondary efficacy outcomes (modified intention-to-treat population)

	KIN001 (n=63)	Placebo (n=65)	Total (n=128)
Patients alive and without any oxygen support during the 4-week treatment period	19 (29·2%)	21 (33·3%)	40 (31·3%)
Number of days alive and without any oxygen or ventilatory support during the 4-week treatment period[a]	24 (20–28)	24 (20–28)	24 (20–28)
Most advanced treatment during the 28-day treatment period			
Low dose oxygen	37 (56·9%)	38 (60·3%)	75 (58·6%)
HFNC[b] / NIV[c]	4 (6·2%)	4 (6·3%)	8 (6·3%)
Invasive MV[d]	2 (3·1%)	0	2 (1·6%)
ECMO[e]	0	0	0
Death	3 (4·6%)	0	3 (2·3%)

Results are presented as count (%) or median (25–75th percentile).
[a]Death outcome is calculated as −1.
[b]HFNC: High-Flow nasal cannula.
[c]NIV: non-invasive ventilation.
[d]MV: mechanical ventilation.
[e]ECMO: extracorporeal membrane oxygenation.

group and, all considered by the DSMB to be related to disease severity and consequent multiple organ failure, and not related to treatment. During the treatment period, there were no difference in the changes in liver enzymes between the two treatment arms (Table 3). Additionally, there were no differences in hemoglobin, platelet count, creatinine, blood glucose, amylase, bilirubin, and alkaline phosphatase values between the two groups.

DISCUSSION

KINETIC represents the first-in-human use of KIN001, a combination of pamapimod and pioglitazone, administered to non-critically ill hospitalized COVID-19 patients to decrease the risk of progression to severe ARF.

Over the last year, many clinical studies in hospitalized, non-critically ill COVID-19 patients have reported a decrease in mortality and need for advanced respiratory support, leading to frequent negative results.[12–25] This is due to several factors: the global level of immunity increased due to vaccination and widespread infection, dexamethasone therapy was widely introduced for the treatment of hospitalized patients, and the quality of care improved, partly due to lower numbers of hospitalized patients that made more resources available for their care. Consequently, the number of oxygen-free days have been proposed to be the most clinically relevant outcome for studies in hospitalized COVID-19 patients.[26] The KINETIC endpoints were amended to reflect this evolution and the interim analysis was consistent with this trend. Despite this amendment, no signal of a positive effect of KIN001 could be detected, and the trial was prematurely terminated for futility.

Table 3. Change of inflammatory markers and liver enzymes values by treatment group in the intention-to-treat population

	Inflammatory markers				Liver enzymes			
	CRP[a]		WBC[b]		AST[c]		ALT[d]	
	Placebo	KIN001	Placebo	KIN001	Placebo	KIN001	Placebo	KIN001
Inclusion	37 (16–68)	34 (15–71)	6·2 (4·1–7·6)	6·6 (4·9–9·0)	43 (28–52)	39 (28–52)	34 (23–48)	35 (27–49)
Day 4	9 (3–20)	8 (3–19)	7·4 (5·5–9·4)	7·9 (5·9–10·3)	38 (28–66)	41 (31–68)	53 (32–87)	56 (34–93)
Day 7	3 (1–11)	4 (1–17)	7·6 (5·9–9·9)	8·2 (6·4–11·1)	34 (23–56)	31 (24–42)	51 (31–86)	49 (29–89)
Day 14	2 (1–7)	3 (1–10)	6·6 (5·4–9·1)	7.7 (5·9–10·9)	30 (22–40)	30 (21–43)	43 (27–64)	47 (28–73)
Day 28	2 (0–9)	3 (1–9)	6.5 (5·0–7·4)	6·7 (5·6–8·0)	26 (21–33)	26 (19–34)	33 (20–46)	31 (22–44)
Day 56	3 (1–5)	3 (1–5)	6·7 (5·9–8·0)	6·8 (5·6–8·8)	25 (21–32)	25 (18–35)	26 (21–37)	30 (20–40)

Results are presented as median (25–75th percentile).
[a]CRP: C-reactive protein (mg/l).
[b]WBC: white blood cells (G/l).
[c]AST: aspartate aminotransferase (U/l).
[d]ALT: alanine aminotransferase (U/l).

Table 4. Safety analysis during 4 weeks by treatment arm, with number (%) of patients with at least one adverse event, in the intention-to-treat population

	KIN001 (n=68)	Placebo (n=64)	Total (n=132)
Any AE[a]	43 (63·2%)	42 (65·6%)	85 (64·4%)
Death related to AE	3 (4·4%)	0 (0%)	3 (2·3%)
Severe AE	8 (11·8%)	2 (3·1%)	10 (7·6%)
Interruption of therapy	3 (4·4%)	0 (0%)	3 (2·3%)
Withdrawal of drug therapy	8 (11·8%)	1 (1·6%)	9 (6·8%)
Possible drug-related AE	2 (2·9 %)	0	2 (1·5 %)
Maximum severity of AE:			
Mild	34 (50·0%)	35 (54·7%)	69 (52·3%)
Moderate	20 (29·4%)	20 (31·3%)	40 (30·3%)
Severe	6 (8·8%)	1 (1·6%)	7 (5·3%)
Number and type of adverse event during the 4-week treatment period	43 (63·2%)	42 (65·6%)	85 (64·4%)
Supplementary investigations needed	6 (8·8%)	8 (12·5%)	14 (10·6%)
Infections	6 (8·8%)	2 (3·1%)	8 (6·1%)
Vascular disorders	1 (1·5%)	5 (7·8%)	6 (4·5%)
Nervous system disorders	2 (2·9%)	3 (4·7%)	5 (3·8%)
Respiratory, thoracic, and mediastinal disorders	5 (7·4%)	0 (0%)	5 (3·8%)
Cardiac disorders	3 (4·4%)	1 (1·6%)	4 (3%)
Metabolism and nutrition disorders	2 (2·9%)	2 (3·1%)	4 (3%)
Gastrointestinal disorders	2 (2·9%)	1 (1·6%)	3 (2·3%)
Psychiatric disorders	2 (2·9%)	1 (1·6%)	3 (2·3%)
Renal and urinary disorders	2 (2·9%)	1 (1·6%)	3 (2·3%)
Eye disorders	0 (0%)	2 (3·1%)	2 (1·5%)
Skin and subcutaneous tissue disorders	2 (2·9%)	0 (0%)	2 (1·5%)
Blood and lymphatic system disorders	1 (1·5%)	0 (0%)	1 (0·8%)
Administration site conditions	1 (1·5%)	0 (0%)	1 (0·8%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (1·6%)	1 (0·8%)

[a]AE: adverse event.

The high proportion of the co-administered therapies with a proven clinical efficacy in hospitalized patients is probably at least partially responsible for the low incidence of progression to severe disease in our population. Of note, slightly more patients in the placebo arm were treated with a double or triple combination therapy, which might explain the absence of detectable effect of KIN001, although the small numbers and the absence of stratification on this parameter do not allow a statistical comparison.

Importantly, KIN001 was well-tolerated in this at-risk population of hospitalized patients, with no increase in the incidence of adverse events compared to placebo. In particular, no sign of liver or renal toxicity was detected, and this important finding complements data from prior clinical studies of pamapimod as monotherapy for the treatment of rheumatoid arthritis.[4,5]

Limitations of the study

The KINETIC trial had several limitations. First, due to the decrease in the incidence of COVID-19 progression to severe ARF and death, the trial was underpowered to show a decrease in mortality or need for MV. Second, a large proportion of patients were recruited in a single country during a relatively short period of time, which may not be representative of the hospitalized COVID-19 patient population globally. Eventually, a high proportion of patients were hospitalized with WHO category 4 at inclusion, with a favorable outcome observed for most, resulting in a small contribution to the incidence of the amended primary endpoint.

The progression of SARS-CoV-2 infection is characterized by successive phases; viral replication, followed by an acute inflammatory response, and longer-term effects on organ function and fibrosis.[27,28] In hospitalized patients with moderate COVID-19, the viral replication phase may already be in decline, such that the potential impact of the antiviral activity of KIN001 could not be fully realized. Similarly, the

impact of the anti-fibrotic activity of KIN001 would be evident only upon radiological or functional assessments and, therefore, difficult to evaluate in KINETIC due to the length of the study and the lack of specific assessments.

In conclusion, the KINETIC trial has shown that KIN001, the oral combination of pamapimod and pioglitazone, is safe and well-tolerated in hospitalized COVID-19 patients but has no impact on the risk of progression to severe disease in this population. KIN001 is currently under evaluation in a second phase two, randomized, placebo-controlled trial (KINFAST - KIN001 For Accelerated Symptoms Termination) in outpatients, to assess its potential to reduce the severity and duration of symptoms. It may be worthwhile to explore the potential usefulness of KIN001 in other indications characterized by inflammation and fibrosis.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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An independent statistician, Tim Farley, reviewed and interpreted the statistical analysis, and reviewed the final draft of the manuscript.

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AUTHOR CONTRIBUTIONS

A.B., M.W., C.B., and T.F. conceived and designed the study. C.B. and T.F. collected the data in collaboration with the CRO. C.B. and T.F. accessed and verified the data. U.V. and I.S. did the statistical analysis. T.F. and C.B. interpreted the data. T.F. wrote the first draft of the manuscript, and all authors provided critical review, revised the text, and approved the final version for publication. All authors had full access to all study data and accept the final responsibility for the decision to submit for publication. M.J.G.T.V., as principal investigator, reviewed and approved the protocol, revised and approved the manuscript.

DECLARATION OF INTERESTS

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Trial registration (EUDRACT)	N/A	2020-005849-16
Other		
Ethics Committee approval (Russia)	N/A	Ministry of Healthcare of the Russian Federation Authorization number: 753 (18.11.2021)
Ethics Committee approval (Bulgaria)	N/A	Republic of Bulgaria, Ministry of Health, Committee for Clinical Trials Outgoing Number: CT 1075 / 18-11-2021 EKKI-4796/09.122021r
Ethics Committee approval (Germany)	N/A	Ethikkommission des Fachbereichs Medizin Universitätsklinikum der Goethe-Universität AS 20/2021
Ethics Committee approval (Hungary)	N/A	Medical Research Council – Budapest 22423-2

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Thierry Fumeaux (thierry.fumeaux@kinarus.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Any additional information required about the data reported in this paper is available from the lead contact upon request. In particular, individual level of data from the study can be obtained from the lead author via request. This paper does not report any original code.

ADDITIONAL RESOURCES

The KINETIC trial is registered as EudraCT Number 2020-005849-16. The final version of the full protocol is available upon request to the lead contact.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

KINETIC was a multicentre, randomised, double-blind, placebo-controlled, phase two trial, conducted in 13 centres in three countries (Bulgaria two sites, Germany six sites, and Russia five sites). The study protocol was approved by national and regional ethics committees, in Germany, Bulgaria, and Russia. The protocol was amended three times for minor changes (new country and study sites, and timing of the interim analysis). A fourth amendment was required due to the evolution of the pandemic, with the adaptation of primary and secondary endpoints. The final version of the protocol is available on demand. The trial is registered as EudraCT Number 2020-005849-16.

The study population consisted of female and male hospitalised adult patients with moderate COVID-19, defined by the WHO Clinical Progression Scale (score of four with comorbidities or score of five).[11] COVID-19 was confirmed by RT PCR or rapid antigen-test, according to local availability and policy. Exclusion criteria were known allergy to the components of KIN001, current pregnancy, contraindication to pioglitazone (cardiac failure or bladder cancer), and an active viral (other than SARS-CoV-2), bacterial, or fungal infection. All participants signed a written informed consent. Information regarding ancestry, race, and/or ethnicity, was not recorded.

Key data and resources table are available upon demand to the lead contact person.

METHOD DETAILS

Within three days after screening, participants who signed the informed consent were randomized 1:1 to oral KIN001 (pamapimod 150 mg – pioglitazone 10 mg) or matching placebo, both added to standard of care, via an interactive web response system (IWRS) according to a list generated by an independent statistician. Block randomization (size of four) and stratification per country and per age ($\leq$ 65 years, > 65 years)

were used. Since vaccines were not broadly available at the start of the study, vaccination status was not included for stratification. The assigned a treatment number of each patient corresponded to a study drug kit for the entire 28-day treatment period, each kit containing two packages of tablets, one with either pamapimod (75 mg, treatment group) or matching placebo (control group), and the other with pioglitazone (5 mg, treatment group) or matching placebo (control group). Patients were enrolled and assigned to intervention by the local investigator. All participants and care providers were blinded to the intervention, Outcomes were assessed in a blinded fashion.

At inclusion, patient's medical history, SARS-CoV-2 infection confirmation tests, and WHO Clinical Progression score were recorded, and blood was sampled for laboratory tests. Oral KIN001 or placebo tablets were taken twice daily for 28 days, including the period after hospital discharge. The follow-up period was 4 weeks, with an end visit at eight weeks.

The asigned treatment was added to the local standard of care, in line with the updated WHO guidelines regarding other drug therapies. In particular, corticosteroids, monoclonal anti-Interleukin-6 antibodies and Janus Kinase inhibitors could be prescribed to patients, but non-recommended or experimental drug therapies were discouraged. Oxygen and ventilatory support modalities were prescribed by the physician in charge, in accordance with local guidelines.

Patient evaluations (vital signs and physical examination, determination of WHO progression score, and blood sampling) were conducted at four timepoints during treatment and at the end visit at eight weeks, when both drug packages were returned. All events that occurred between each visit were recorded and reported to the local investigator. Adverse events and serious adverse events were immediately reported to the Sponsor.

QUANTIFICATION AND STATISTICAL ANALYSIS

The primary efficacy endpoint was initially the proportion of patients progressing to death or severe ARF needing invasive MV or ECMO. This endpoint was amended before the first interim efficacy analysis to adapt to the evolution of the pandemic seen in contemporary observational and interventional studies, as the proportion of patients progressing to death or MV had significantly decreased. A blinded analysis of the overall incidence of the original primary endpoint by an independent Data Safety Monitoring Board (DSMB) in 136 included patients confirmed that the overall incidence of the primary endpoint (10%) was lower than expected (18%), and that a large increase in patient sample would be needed to maintain 80% power to detect significant differences between groups. This would have been a challenge, given the low rate of recruitment seen in COVID-19 clinical trials after the initial waves.

The risk of reduction in disease severity was anticipated in the design of the key secondary endpoint, which was defined as the number of days alive and free of any advanced ventilatory support (NIV, MV, or ECMO) at 28 days. The DSMB blinded analysis also showed that the sample size would also be insufficient to maintain the statistical power for this endpoint too, and the protocol was therefore amended. The newly defined primary endpoint was the proportion of patients alive and free of any oxygen or respiratory support (conventional oxygen, HFNC, NIV, MV or ECMO) during the 28-day study period, as proposed by the ACTIV-4 platform trial.[26] The revised secondary endpoint was the number of days alive and free of any oxygen or respiratory support during the 28-day treatment. Safety outcomes were the incidence and severity of adverse events, of serious adverse events, and death, as well as drug and study discontinuations due to adverse events.

The sample size was initially based on a 23% incidence of the primary endpoint in the control group and a 45% reduction in the active arm (13%, corresponding to an Odds Ratio (OR) of 2·0). After the amendment of the primary endpoint, the Sponsor proposed to target the same OR 2·0 for the proportion of patients reaching the endpoint in the treated group. A blinded safety review was planned after 40 participants had completed the eight-week observation and an interim efficacy analysis was planned after 144 patients had completed the study. Due to slow recruitment, June 1st, 2022, was selected as the closing date for this efficacy interim analysis. The statistical analysis was conducted by an independent statistician, in intention-to-treat, in the sample of patients who had completed the 8-week observation, with the approach proposed by the ACTIV-4 investigators.[26] A conditional power calculation was planned to assess probability of achieving a positive effect with the originally planned sample size.[29] Based on this, the DSMB was instructed to either propose to stop the trial for strong evidence of efficacy, for safety concerns, or for futility, or to propose to adapt the sample size accordingly.

Results are presented as count (%), mean $\pm$ standard deviation or median (25-75th percentile) depending on data type and distribution. Pearson chi square test was used to assess the difference in the primary endpoint between groups. Results are presented in tables and graphs. All data were analysed using SPSS 29.0 statistical software (Armonk, NY: IBM Corp).