Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among patients with COVID-19, should imatinib be used for treatment?

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RECOMMENDATION

There is insufficient evidence to recommend the use of imatinib among patients with COVID-19 infection. *(Low certainty of evidence)*

Consensus issues
Further trials are needed to recommend the use of imatinib for the treatment of COVID-19.

Key Findings

There is one (1) randomized controlled trial (RCT) that investigated the effect of imatinib compared to placebo as treatment for hospitalized patients with COVID-19 requiring supplemental oxygen. Imatinib was associated with significant reduction in the duration of mechanical ventilation and duration of intensive care unit (ICU) stay. However, there was no significant benefit for several outcomes such as mortality at day 28, need for ICU admission, need for mechanical ventilation, discontinuation of supplemental oxygen and mechanical ventilation, discontinuation of ventilation and supplemental oxygen in 48 hours, and duration of hospital admission. There was also no significant difference in the number of adverse events. The overall certainty of evidence was rated low; evidence was downgraded for serious risk of bias and imprecision due to wide confidence intervals and small number of events.

Introduction

Imatinib is an oral anti-cancer agent that inhibits the activity of some tyrosine kinases originally designed to treat Chronic Myeloid Leukemia.[1] Although imatinib was originally designed to inhibit the BCR-Abl fusion protein, it also inhibits several other kinases including c-Abl, Abl-related gene (Arg), c-kit, and platelet-derived growth factor receptor (PDGFR). These kinases are involved in regulating vascular permeability, suggesting that imatinib may have a potential role in attenuating inflammation and restoring vascular integrity in inflammatory leak syndrome.[2] Imatinib has also shown in vitro anti-viral properties against severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which are phylogenetically related to SARS-CoV-2.[3]

Imatinib can be useful for treating pneumonia from SARS-CoV-2 infection, as it has shown promise in treating pulmonary diseases.[4] It improved the status of patients with pulmonary and systemic vascular leak.[5] Imatinib has been found to prevent pulmonary damage by reducing tissue edema and maintaining endothelial barrier integrity in murine models of acute inflammatory lung injury.[6]

Review Methods

A systematic search was done on September 10 to 11, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and imatinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries. Preprints were also searched using medrxiv, chinaxiv and biorxiv. Only randomized controlled trials that compared imatinib against placebo or standard of care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, need for mechanical ventilation, hospital length of stay, time to clinical improvement or recovery, improvement in radiographic findings, virologic clearance by PCR test, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of imatinib.

Results

We found one (1) randomized double-blind, placebo-controlled trial that included a total of 400 COVID-19 patients in 13 hospitals followed-up for 28 days.[7] The study recruited hospitalized patients requiring supplemental oxygen administration and compared the use of imatinib with placebo in treating COVID-19, with all study participants receiving standard of care. The median age of the participants was 64 years and 69% were male. The characteristics of the included study are summarized in Appendix 3.

The overall certainty of evidence was rated low due to serious risk of bias and imprecision due to wide confidence intervals and small number of events. There were issues with selection and attrition bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

There was no significant difference in the number of patients who discontinued supplemental oxygen and mechanical ventilation for more than 48 consecutive hours in the imatinib group and placebo group (RR 1.07, 95% CI 0.96,1.19). There was also no significant difference in the discontinuation of supplemental oxygen and mechanical ventilation (HR 1.07, 95% CI 0.62,1.84).

The imatinib group had significantly reduced risk of mortality at day 28 compared to the placebo group (RR 0.53, 95% CI 0.29, 0.96). However, there was no significant difference in mortality after adjustment for baseline imbalances (adjusted HR 0.52, 95% CI 0.26, 1.05). There was no significant difference in need for intensive care unit admissions (RR 1.13, 95% CI 0.74, 1.71) and need for mechanical ventilation (RR 0.98, 95% CI 0.76, 1.25; adjusted HR 1.02, 95% CI 0.80, 1.30).

The median duration of mechanical ventilation was significantly shorter for the imatinib group at 7 days (IQR 3-13) compared with the placebo group at 12 days (IQR 6-20), p-value = 0.008. The duration of hospital admission was not significantly different with a median of 7 days (IQR 4-11) for the imatinib group and 6 days (IQR 3-11) for the placebo group, p-value = 0.51. The median duration of ICU stay for the imatinib group was also significantly shorter at 8 days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21), p-value = 0.025.

Adverse events

The study also measured safety outcomes as occurrences of Grade 3, 4, and 5 adverse events (Grade 3 is categorized as severe or medically significant but not immediately life-threatening; Grade 4 means life-threatening consequences indicating urgent intervention; and Grade 5 is death). The number of adverse events did not differ significantly in the treatment and

placebo arms (RR 1.06, 95% CI 0.85, 1.32). The most common Grade 3 adverse events were thromboembolic events, decrease lymphocyte counts, alkalosis, and hyperglycemia while the most frequent Grade 4 adverse event was acute respiratory distress syndrome or ARDS.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian COVID-19 Guidelines (version 43.0, as of September 29, 2021)	The panel deems the evidence as insufficient to promote the use of imatinib outside of clinical trials, and is awaiting publication of additional studies before developing a recommendation.[10]
World Health Organization Living Guidelines (as of September 24, 2021)	No recommendations on imatinib as treatment for COVID-19.[11-13]
NIH COVID-19 Guidelines (as of October 7, 2021)	
Infectious Diseases Society of America (IDSA) Guidelines on Treatment and Management of Patients with COVID-19 (as of October 1, 2021)	

Imatinib is 1 of the 3 new medications included in the SOLIDARITY Plus Trial [14], which is currently ongoing in 52 countries.

Research Gaps

There are 11 studies registered in various clinical trial registries, 1 of which was prematurely ended due to undisclosed reasons. There are 2 studies evaluating intravenous imatinib and 6 studies involving the oral route. The doses of the treatment arms range from 200 to 800mg given for 14 to 21 days. The characteristics of ongoing studies are summarized in Appendix 6.

References

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 6)

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (6)	Small	Uncertain			• Reduced risk of mortality at day 28 (RR 0.53, 95% CI 0.29-0.96) but no difference in mortality after baseline adjustment for imbalance (adjusted HR 0.52, 95% CI 0.26-1.05) • Shorter median duration of mechanical ventilation at 7 days (IQR 3-13) at 12 days (IQR 6-20), p-value = 0.008 • Median duration of ICU stay was shorter at 8 days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21), p-value = 0.025
Harm	Large	Small (4)	Uncertain (2)				• The number adverse events did not differ significantly in the treatment and placebo arms (RR 1.06, 95% CI 0.85-1.32).
Certainty of Evidence	High	Moderate (1)	Low (5)	Very low			• Low due to very serious issues with imprecision in 6 critical outcomes and a very small sample size
Balance of effects	Favors drug	Does not favor drug (5)	Uncertain (1)				• Imatinib was associated with significant benefit in mortality at day 28, duration of mechanical ventilation, and duration of intensive care unit (ICU) stay • No significant difference in the number of adverse events
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (4)	Negligible cost	Moderate savings (2)	Large savings	• One 100mg tablet of imatinib costs Php 125.89 and the total cost of treatment per patient is Php 5,539.16 when given for 10 days
Certainty of evidence of required resources	No included studies	Very low (2)	Low (2)	Moderate (1)	High (1)		
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (3)	Reduced (1)	Probably no impact	Increased (2)			
Acceptability	Uncertain (5)	No	Yes (1)				
Feasibility	Uncertain (5)	No	Yes (1)				

Appendix 2. Search and Yield Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline https://pubmed.ncbi.nlm.nih.gov/	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND IMATINIB	Sept 11,2021	46	3
CENTRAL https://www.cochranelibrary.com/advanced-search	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND IMATINIB	Sept 10,2021	18 trials	11
Google Scholar	coronavirus, SARS COV 2,COVID-19, Imatinib	Sept 10,2021	407	2
COVID-NMA initiative https://covid-nma.com/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	1	1
ClinicalTrials.gov https://clinicaltrials.gov/	coronavirus, SARS COV 2,COVID-19, Imatinib	Sept 11,2021	6	6
Chinese Clinical Trial Registry http://www.chictr.org.cn/searchprojen.aspx	coronavirus, SARS COV 2 COVID-19, Imatinib	Sept 10,2021	0	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 11,2021	8	5
Republic of Korea – Clinical Research Information Service https://cris.nih.go.kr/cris/info/introduce.do?search_lang=E&lang=E	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0

https://rctportal.niph.go.jp/en/				
CenterWatch https://www.centerwatch.com/clinical-trials/listings/	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
chinaxiv.org	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 10,2021	0	0
Medrxiv.org	coronavirus, SARS COV 2, COVID-19, Imatinib	Sept 11,2021	14	0
Biorxiv.org	coronavirus, SARS COV 2 COVID-19, Imatinib	Sept 11,2021	34	0

Appendix 3. Characteristics of Included Study

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Imatinib in patients with severe COVID-19: A randomized, double blind, placebo controlled, clinical trial *Aman et al., 2021*	N = 400 1. 18 years old and above 2. Hospitalized patients with COVID-19 requiring supplemental oxygen Duration of follow-up: 28 days	Experimental: Imatinib 800mg loading dose (day 0) then 400mg once daily (days 1 to 9) Control: Placebo	Primary: Time to discontinuation of ventilation and supplemental oxygen for more than 48 hours Secondary: Mortality at 28 days, ICU admissions, length of ICU and hospital admission, and need for and duration of mechanical ventilation	Randomized Double-blind Placebo-controlled

Appendix 4. Study Appraisal

Aman et al. 2021

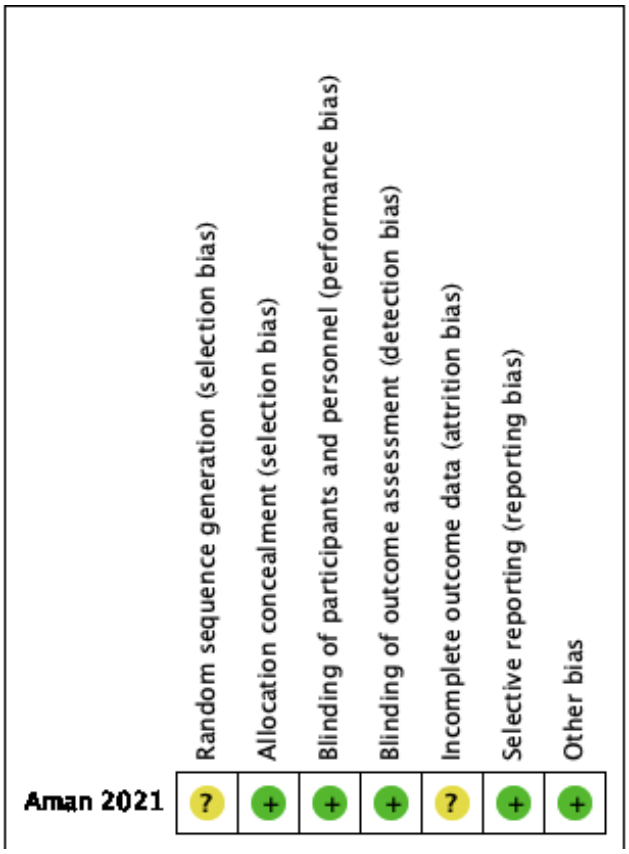

Figure 1. Risk of bias summary table

Appendix 5. GRADE Evidence Profile

Author(s): Fides Roxanne M. Castos, MD
Question: Imatinib compared to Standard of Care or Placebo for Covid-19 Infection
Setting: In-hospital
Bibliography: Aman, J., Duijvelaar, E., Botros, L., Kianzad, A., Schippers, J., Smeele, P., Azhang, S., Bartelink, I., Bayoumy, A., Bet, P., Boersma, W., Bonta, P., Boomars, K., Bos, L., van Bragt, J., Braunstahl, G., Celant, L., Eger, K., Geelhoed, J., van Glabbeek, Y., Grotjohan, H., Hagens, L., Happe, C., Hazes, B., Heunks, L., van den Heuvel, M., Hoefsloot, W., Hoek, R., Hoekstra, R., Hofstee, H., Juffermans, N., Kemper, E., Kos, R., Kunst, P., Lammers, A., van der Lee, I., van der Lee, E., Maitland-van der Zee, A., Mau Asam, P., Mieras, A., Muller, M., Neefjes, E., Nossent, E., Oswald, L., Overbeek, M., Pamplona, C., Paternotte, N., Pronk, N., de Raaf, M., van Raaij, B., Reijrink, M., Schultz, M., Serpa Neto, A., Slob, E., Smeenk, F., Smit, M., Smits, A., Stalenhoef, J., Tuinman, P., Vanhove, A., Wessels, J., van Wezenbeek, J., Vonk Noordegraaf, A., de Man, F. and Bogaard, H., 2021. Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. The Lancet Respiratory Medicine, 9(9), pp.957-968.

Certainty Assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Imatinib	Standard of Care or Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (D28)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/197 (7.6%)	27/188 (14.4%)	**HR 0.52** (0.26 to 1.05)	**66 fewer per 1,000** (from 104 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
Discontinuation of oxygen support/Mechanical Ventilation for >48 hours												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	160/197 (81.2%)	143/188 (76.1%)	**RR 1.07** (0.96 to 1.19)	**53 more per 1,000** (from 30 fewer to 145 more)	⨁⨁◯◯ LOW	CRITICAL
Admitted to the ICU												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	39/197 (19.8%)	33/188 (17.6%)	**RR 1.13** (0.74 to 1.71)	**23 more per 1,000** (from 46 fewer to 125 more)	⨁⨁◯◯ LOW	CRITICAL
Need for Intubation and Mechanical Ventilation												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	30/197 (15.2%)	26/188 (13.8%)	**HR 1.02** (0.80 to 1.30)	**3 more per 1,000** (from 26 fewer to 38 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse Events												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	91/197 (46.2%)	82/188 (43.6%)	**RR 1.06** (0.85 to 1.32)	**26 more per 1,000** (from 65 fewer to 140 more)	⨁⨁◯◯ LOW	IMPORTANT
Duration of Mechanical ventilation												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Median duration of mechanical ventilation was shorter for the imatinib group at 7 days (IQR 3-13) compared with the placebo group at 12 days (IQR 6-20) with a p value of 0.008				⨁⨁◯◯ LOW	IMPORTANT

Length of Hospital Admission

1	randomised trials	serious[a]	not serious	not serious	serious[b,d]	none	Median duration of hospital admission was 7 days (IQR 4-11) for the Imatinib group and 6 dyas (IQR3-11) for the placebo group with a p value of 0.51	⨁⨁◯◯ LOW	IMPORTANT

Duration of ICU admission

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Median duration of ICU stay for the Imatinib group was shorter at 8days (IQR 5-13) compared to the placebo group at 15 days (IQR 7-21) with a p value of 0.025	⨁⨁◯◯ LOW	IMPORTANT

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. selection and attrition bias
b. only 1 study used, n =400
c. wide confidence interval, only 1 study used, n =400
d. p value not significant

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (N)	Interventions	Outcomes	Method
1.Randomized Double-Blind Placebo-Controlled Trial on the Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19	Target N = 204 1. Hospitalized patients 2. ⩾ 18 years of age 3. Positive RT-PCR assay for SARS-CoV-2 in the respiratory tract sample	Experimental: Imatinib oral 400mg daily for 14 days Control: Placebo oral tablet for 14 days	Improved Clinical status on an 8-category ordinal scale	Randomized Parallel assignment Open label
2. A Randomized, Double-blind, Multicentre 2-arm, Parallel-group, Placebo-controlled Study to Investigate the Efficacy and Safety of Intravenous Imatinib Mesylate in Reducing the Severity of Hypoxemic Respiratory Failure in Patients with Critical COVID-19 Receiving Standard of Care.	Target N = 84 1. ⩾18 years 2. negative serum pregnancy test to confirm eligibility 3. SARS-CoV-2 infection confirmed by RT-PCR laboratory test 4. Moderate - severe ARDS 5.Requires intubation or is currently intubated and has been for ⩽ 48 hours	Experimental: Intravenous imatinib mesylate Control: Intravenous placebo-matched	Change from baseline in Oxygen Saturation Index (OSI) at day 10	Randomized Parallel assignment Triple masking
3. Prospective, Phase II, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy of Baricitinib, Imatinib or Supportive Treatment in Patients With SARS-CoV-2 Pneumonia	N = 168 1. ≥ 18 years 2. Confirmed diagnosis Pneumonia COVID-19 3. ECOG functional state 0 or 1 4. Less than 10 days from onset of symptoms 5. No contraindication for medication 6. ECG QT < 440 ms males and < 460 ms females 7. Adequate liver, kidney and hematological function (or within the safety range to use these drugs)	Experimental: Imatinib 400mg Baricitinib 4mg Control: Supportive treatment	Primary Outcome: Clinical Improvement Secondary: Safety and Tolerability of treatments	Randomized Parallel assignment Open label
4. A Randomized, Double-blind, Placebo-controlled Study to Investigate the Safety and Efficacy of Intravenous Imatinib Mesylate (Impentri®) in Subjects with Acute Respiratory Distress Syndrome Induced by COVID-19	Target N = 90 1. Age ≥ 18 years 2. Moderate-severe ARDS, 3. PCR positive for SARS-CoV-2 within the current disease episode	Experimental: Intravenous imatinib mesylate Control: Intravenous placebo solution	Primary: Change in extravascular lung water index (EVLWi) between day 1 and day 4, measured by PiCCO catheter	Randomized Double-blind parallel-group placebo-controlled multi-centre

5. Imatinib for the Treatment of SARS-CoV-2 Induced Pneumonia: A Pilot Study	Target N = 30 1. Age ≥ 18 years 2. PCR positive for SARS-CoV-2 3. Hospitalized with moderate to severe respiratory symptoms as assessed by the Egyptian Ministry of Health National Guidelines	Experimental: Imatinib standard dose 400mg oral tablet once daily for 21 days + standard of care Imatinib low dose 200mg oral tablet once daily for 21 days + standard of care Control: Standard of care	Proportion of patients with COVID-19 pneumonia progressed to critical illness in need for invasive mechanical ventilation	Randomized Parallel assignment Open-label
6. A Randomized Non-Comparative Phase 2 Pilot Study Testing the value of Imatinib Besylate as an early treatment of COVID-19 Disease in aged hospitalized patents	Target N = 99 1. Age > 70 years 2. COVID-19 disease by SARS-CoV-2 RT-PCR 3. ≤ 7 days of COVID-19 disease 4. Non-severe COVID-19	Experimental: Imatinib 800 mg/day for 14 days Control: Standard of care	Prevention of severe COVID-19 disease in hospitalized aged patients. [Time Frame: 30 days] 30 day-mortality rate in aged patients hospitalized with COVID-19	Randomized Parallel assignment Open-label
7. COUNTER-COVID - Oral imatinib to prevent pulmonary vascular leak in COVID-19 – a randomized, double-blind, placebo controlled, clinical trial in patients with severe Covid19 disease	N = 386 1. Age > 18 years 2. Hospital admission with proven SARS-CoV-2 infection 3. Hypoxemic respiratory failure (SaO2 <94%, PaO2 <9kPa)	Experimental: Imatinib (oral) Control: Placebo	Time to liberation from ventilation and supplemental oxygen > 48 hours while being alive during a 28-day period after randomization	Randomized Controlled Parallel Double-blind
8. WHO SOLIDARITY Finland: The multicenter trial on the efficacy of different anti-viral drugs in SARS-CoV-2 infected patients (COVID-19)	N = 1,164 1. Age ≥ 18 years 2. Laboratory-confirmed SARS-2-CoV-2 infection 3. Admitted to the hospital ward or the ICU 4.No anticipated transfer within 72 hours to a non-study hospital	Experimental: Imatinib (oral) Artesunate Vs. Infliximab	In-hospital Mortality	Randomized Controlled Open label
9. Home treatment of elderly patients with symptomatic SARS-CoV-2 infection (COVID-19): a multiarm, multi-stage (MAMS) randomized trial to assess the efficacy and safety of several experimental treatments to reduce the risk of hospitalization or death (COVERAGE trial)	N = 1,057 1. Age ≥ 60 years old 2. Positive SARS-CoV-2 test on nasopharyngeal swab 3. Onset of symptoms < 5 days prior to swabbing 4. Valid, ambulatory person, fully capable of understanding the challenges of the trial 5. No hospitalization criteria 6. Covered by health insurance	Experimental: Imatinib 400mg Telmisartan 20mg Favipiravir 200mg Control: Vitamin supplements	Proportion of participants with an occurrence of hospitalization and/or death between D0 and D14 in each arm	Randomized Controlled Parallel Open

10. A proof of concept study testing the value of Imatinib in prevention of Covid 19 in aged patients Note: Prematurely ended	Target N = 382 Prevention of severe COVID-19: 1. Resident living in an open nurse home 2. Resident without symptom of COVID-19 3. No imatinib contra-indication Prevention of severe COVID-19: 1. Patient aged > 70y 2. Patient with a documented SARS-CoV-2 infection (if no test is available, suspected SARS-CoV-2 infection). 3. Initial phase (7 days) of COVID-19	Experimental: Imatinib oral Control: Standard follow-up	Prevention of SARS-CoV-2 infection Prevention of severe COVID-19 disease	Randomized Control Open trial