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## Concerns about pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) studies in the new therapeutic area of COVID-19 infection

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1 **Concerns about pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-**  
2 **PD) studies in the new therapeutic area of COVID-19 infection**

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51 **Keywords** : COVID-19 ; Pharmacokinetics ; Pharmacodynamics ; PK-PD

52

53 *Abstract*

54 In the context of the COVID-19 pandemic, several drugs have been repurposed as potential  
55 candidates for the treatment of COVID-19 infection. While preliminary choices were  
56 essentially based on in vitro potency, clinical translation into effective therapies may be  
57 challenging due to unfavorable in vivo pharmacokinetic properties at the doses chosen for this  
58 new indication of COVID-19 infection. However, available pharmacokinetic and  
59 pharmacokinetic-pharmacodynamic studies suffer from severe limitations leading to  
60 unreliable conclusions, especially in term of dosing optimization.

61 In this paper we propose to highlight these limitations and to identify some of the major  
62 requirements that need to be addressed in designing PK and PK-PD studies in this era of  
63 COVID. A special attention should be paid to pre-analytical and analytical requirements and  
64 to the proper collection of covariates affecting dose-exposure relationships (co-medications,  
65 use of specific organ support techniques and other clinical and para-clinical data). We also  
66 promote the development of population PK and PK-PD models specifically dedicated to  
67 COVID-19 patients since those previously developed for other diseases (SEL, malaria, HIV)  
68 and clinical situations (steady-state, non-ICU patients) are not representative of severe  
69 patients.

70 Therefore, implementation of well-designed PK and PD studies targeted to COVID-19  
71 patients is urgently needed. For that purpose we call for multi-institutional collaborative work  
72 and involvement of clinical pharmacologists in multidisciplinary research consortia.

73

74

75

76 *Introduction*

77 In the context of the COVID-19 pandemic, several existing approved drugs and experimental  
78 antiviral agents have been repurposed as potential antiviral candidates for the treatment of  
79 COVID-19 infection. While preliminary choices were essentially based on *in vitro* potency,  
80 clinical translation into effective therapies may be challenging due to unfavorable *in vivo*  
81 pharmacokinetic (PK) properties (i.e. plasma protein binding, tissue distribution, drug  
82 interactions) at the doses chosen for this new indication of COVID-19 infection. The  
83 particular conditions of COVID-19 infection (cytokine storm, multi-visceral failure and life-  
84 threatening prognosis), patient co-morbidities (i.e. obesity, diabetes, cardiovascular  
85 complications) and the requirement for a short and rapidly effective treatment further  
86 complicate the choice of the ideal candidate.

87 Remdesivir, chloroquine derivatives (essentially hydroxychloroquine (HCQ) due to a better  
88 safety profile than chloroquine) and the anti-HIV agent lopinavir (LPV) were among the first  
89 to be tested due to an *in vitro* antiviral activity demonstrated against SARS-CoV-2 or other  
90 similar respiratory viruses (i.e. SARS-CoV, MERS-CoV). Although remdesivir is not yet  
91 commercially available, other agents are already easily accessible to clinical investigators as  
92 they are part of the therapeutic armamentarium of other diseases (i.e. systemic lupus  
93 erythematosus (SLE) for HCQ and human immunodeficiency virus (HIV) treatment for LPV)  
94 probably explaining the large number of ongoing clinical trials worldwide. Favipiravir,  
95 ribavirin, tocilizumab, ivermectin, nafamostat and other agents have also been proposed for  
96 treatment of COVID-19 infection either as antivirals or immunomodulatory agents (Sanders et  
97 al., 2020).

98 In the area of infectious diseases and antiviral drugs, pharmacological properties are of  
99 particular importance for treatment choices, evaluation and optimization. Indeed, suboptimal

100 antiviral response may be a consequence of inadequate exposure and/or poor PK-PD  
101 properties of the studied drug. From the HIV pandemic, we have learned that maintaining  
102 sufficient plasma drug exposure is critical to stop virus replication and avoid emergence of  
103 resistances (González de Requena et al., 2005). This has led to the implementation of  
104 strategies to optimize dosing regimen such as the PK “boosting”, used in the  
105 lopinavir/ritonavir (LPV/r) association. In this area, increasing knowledge on the PK and  
106 pharmacokinetic-pharmacodynamic (PK-PD) relationships of antiretrovirals has also  
107 demonstrated its usefulness in treatment optimization through the use of therapeutic drug  
108 monitoring (Boffito et al., 2005). In the context of COVID-19 infection, optimizing drug  
109 exposure at the site of infection, *i.e.* in the respiratory tract, is probably the key to successful  
110 treatment.

111

112 Accurate collection of PK and PD data is therefore of primary importance, especially for these  
113 repurposed drugs. We believe that extrapolation of PK data from other clinical situations may  
114 require specific caution due to different physiopathological conditions. In the context of the  
115 current global emergency, the number of clinical trials is rapidly increasing in order to quickly  
116 generate the data required for efficient patient healthcare. However, we have found that some  
117 of the pharmacology data published so far are somewhat disappointing, due to a lack of  
118 information permitting adequate comprehension of the dose-exposure and dose-effect  
119 relationships (Gautret et al., 2020; Perinel et al., 2020) and the poor representativeness of data  
120 used for simulations of effective dosing regimens (Garcia-Cremades et al., 2020; Perinel et  
121 al., 2020; Yao et al., 2020).

122 For these reasons and on behalf of the Clinical Pharmacology Committee of the French  
123 agency for AIDS and viral hepatitis research (ANRS) and the Therapeutic Drug Monitoring

124 and Treatment Personalization working group of the French Society of Pharmacology and  
125 Therapeutics (SFPT), we believe that there is an urgent need for clarifications and  
126 improvements in order to generate high-quality PK and PK-PD data for the drugs to be used  
127 for COVID-19 treatment.

128 *Limitations of available PK and PK-PD data.*

129 Few studies have already described PK and PK-PD in potential treatments for COVID-19  
130 infection and only a small fraction of ongoing clinical trials have planned to do so. We were  
131 only able to find 18 out of the 1546 registered in clinicaltrials.gov (Table I)  
132 (www.clinicaltrials.gov, accessed on: May 18, 2020). The list presented here is representative  
133 of the current situation though not necessarily exhaustive. The situation is particularly striking  
134 for the commonly used repurposed drugs HCQ and LPV for which only 2 trials, one in  
135 children and another in adults, were designed to measure concentration data (Table I). PK  
136 analyses are preferentially planned for new drugs (i.e. monoclonal antibodies) not yet  
137 approved in another indication, such as to take advantage of COVID-19 infection to acquire  
138 PK data in humans. Perinel *et al.* (Perinel et al., 2020) and Gautret *et al.* (Gautret et al., 2020)  
139 have reported HCQ blood or serum concentrations from COVID-19 patients. However, in  
140 these two papers, very little methodological, demographic, clinical, paraclinical and even  
141 dosing information that could help to better understand the dose-exposure relationship in  
142 COVID-19 patients is available. Perinel *et al.* have succinctly described a small population of  
143 intensive care unit (ICU) patients receiving 200 mg of HCQ three times daily without loading  
144 dose in which HCQ whole blood concentrations were measured (Perinel et al., 2020). A  
145 similar dosing regimen was used by Gautret *et al.* (Gautret et al., 2020) but serum  
146 concentrations were determined instead. Apparently, for their study, they have reported the  
147 sum of HCQ and its metabolite concentrations. Whether the approximation used to quantify

148 HCQ metabolite is valid (Gautret et al., 2020) and whether this metabolite is active on SARS-  
149 CoV-2 require further evaluation. Anyway, simply summing-up the concentrations of the  
150 active moiety and its metabolite cannot effectively contribute to comprehension of PK and  
151 PK-PD relationships since they may present different PK and/or PD properties and  
152 consequently misrepresent the adequate drug exposure (Tett, 1993). These preliminary  
153 observations also raise the question of the selection of the adequate biological matrix (blood  
154 vs plasma or serum) for PK assessment of HCQ.

155 Some of these papers (Garcia-Cremades et al., 2020; Perinel et al., 2020; Yao et al., 2020)  
156 have built dosing recommendations for HCQ based on PK models previously developed in  
157 other diseases (SEL, malaria) and clinical situations (steady-state, non-ICU patients), which  
158 raises questions about the relevance of such recommendations. Perinel *et al.* (Perinel et al.,  
159 2020) have graphically compared measured HCQ blood concentrations in COVID-19 patients  
160 to PK simulations obtained with a HCQ population PK model initially developed for  
161 rheumatoid arthritis (RA) patients (Carmichael et al., 2003). Results clearly demonstrate the  
162 inadequacy of a population PK model developed for stable chronic RA patients to describe  
163 actual PK data obtained in ICU patients. This point has also been confirmed by Martin-  
164 Blondel et al (Martin-Blondel et al., n.d.) in their attempt to describe HCQ plasma  
165 concentrations obtained in COVID-19 patients using a PK model initially developed for SLE  
166 patients. As a consequence, we believe that due to probably large PK differences affecting  
167 either clearance or volume of distribution as demonstrated with other anti-infective drugs, this  
168 type of PK model should not be used to simulate any dosing regimens for ICU patients  
169 (Roberts et al., 2014). Whether these models could be applied to less severe COVID patients,  
170 at the early stage of the disease, requires confirmation. It is likely that models developed in  
171 healthy volunteers may be appropriate in the prophylaxis setting. The population PK-PD  
172 model developed by Garcia-Cremades *et al.* (Garcia-Cremades et al., 2020) to describe viral



173 decline and QTc prolongation after HCQ administration in COVID-19 patients, may  
174 theoretically enable achievement of more robust simulation results. For the PK part of the  
175 model, they used a population PK model initially developed using plasma concentrations  
176 obtained from healthy Korean volunteers and Korean patients receiving HCQ for treatment of  
177 vivax malaria (Lim et al., 2009). To demonstrate the adequacy of this model for COVID-19  
178 patients, they used published serum concentrations obtained in non-severe and non-ICU  
179 COVID-19 patients drawn from the study by Gautret *et al.* (Gautret et al., 2020) described  
180 above. Although some differences between serum and plasma concentrations cannot be ruled  
181 out (Bergqvist and Domeij-Nyberg, 1983), they showed that HCQ concentrations from  
182 COVID-19 patients fell within the lower range of expected population profiles, thereby  
183 suggesting that this model could be appropriate to describe the PK of HCQ, at least in non-  
184 ICU COVID-19 patients. However, one should note that the concentration data set used for  
185 this model validation expressed HCQ concentration as the sum of the active moiety and its  
186 metabolite (Gautret et al., 2020), consequently leading to systematic overestimation of actual  
187 exposure to HCQ. Other limitations of this paper apply to the PD parts of the model since  
188 viral kinetic data are from SARS-CoV-1 and the concentration/QTc prolongation data were  
189 obtained from a study with chloroquine. Limitations also apply to the study by Yao *et al.*  
190 (Yao et al., 2020), who developed a PB-PK model to simulate different dosing regimens for  
191 HCQ in COVID-19 patients. Indeed, HCQ concentrations in lung were simulated by  
192 incorporating in their model blood-to-lung concentration data obtained by analyzing tissue  
193 homogenates after dosing in rats (McChesney, 1983). This approach may provide unreliable  
194 diffusion data in lungs (Mouton et al., 2008; Nix et al., 1991) and consequently unreliable  
195 simulations at the site of infection. Similar limitations of this lung model have been discussed  
196 by Fan et al (Fan et al., 2020) and by Yeo et al (Yeo et al., 2020).

197 Similarly, a steady-state population PK model initially developed from HIV patients receiving  
198 standard dose LPV/r has been used to simulate LPV total and free concentrations for  
199 comparison with various virological endpoints, i.e. actual IC50 values for HIV-1, MERS-CoV  
200 and SARS-CoV (Smith et al., 2020). From a PK perspective, this model is probably unable to  
201 describe actual LPV concentrations currently measured in COVID-19 patients, which are as  
202 recently reported (Gregoire et al., 2020) much higher than those observed in HIV patients .  
203 Furthermore, this recent paper showed that despite very high plasma LPV concentrations  
204 observed in patients, the free fraction, representing the active part of the drug, was not  
205 affected (Gregoire et al., 2020).

206 Concerning favipiravir, a recent comment proposes to evaluate higher doses for SARS-CoV-2  
207 than in Ebola disease, based on both *in vitro* EC50 and PK simulations data associated with a  
208 close monitoring of adverse events and plasma concentrations (Eloy et al., 2020). However,  
209 favipiravir is a prodrug, and determination of tissue and intracellular exposure of the activate  
210 metabolite favipiravir-ribofuranosyl-5-triphosphate would be required in order to better  
211 characterize PK-PD relationship (Du and Chen, 2020).

212 No such attempts have been made with remdesivir, yet. Furthermore, data on the diffusion of  
213 these drugs into the pulmonary tract are lacking.

214

#### 215 *Recommendations for improvements*

216 We propose here to identify some of the major requirements that need to be addressed in  
217 designing PK and PK-PD studies in this era of COVID.

#### 218 *Pre-analytical and analytical requirements*

219 Pre-analytical and analytical steps should be strictly controlled to guarantee the necessary  
220 accuracy of measured concentrations. For LPV, well-standardized sampling and assay  
221 procedures have been defined for the monitoring of HIV patients and we believe that these  
222 procedures may adequately apply to COVID-19 patients. By contrast, this is more confusing  
223 with HCQ since it could be analyzed either in whole blood (Carmichael et al., 2003) or in  
224 plasma (Morita et al., 2016; Tett et al., 1989). In the area of anti-infective drugs, plasma may  
225 appear as the preferred matrix since free plasma concentration is in equilibrium with tissue  
226 concentrations and the putative site of action. Moreover, some PK-PD relationships have been  
227 commonly developed for antivirals using plasma concentration as a surrogate for the  
228 concentrations at the site of action (Rizk et al., 2012). However, as regards plasma, it appears  
229 that the pre-analytical step is of particular importance for chloroquine derivatives since early  
230 observations have shown that chloroquine could be released from blood cells, leading to  
231 overestimation of plasma concentrations (Bergqvist and Domeij-Nyberg, 1983). Preliminary  
232 pre-analytical data suggest a similar pattern with HCQ when blood is not rapidly centrifuged  
233 and plasma separated. Moreover, HCQ blood-to-plasma ratio presents wide between-subject  
234 variability according to disease context and equilibrium distribution (Morita et al., 2016; Tett  
235 et al., 1988) suggesting that extrapolation from one to another is not reliable. Pre-analytical  
236 treatment of plasma for remdesivir assay requires an acidic stabilization step (Gilead, personal  
237 communication). Regarding the analytical step, robust specific and sensitive assays targeting  
238 individual analytes (active moiety and metabolites) have already been developed and  
239 validated for clinical pharmacokinetics. In the event of matrix modification (blood vs.  
240 plasma), a partial validation could be considered (European Medicines Agency. Guideline on  
241 bioanalytical method validation, 2011). In addition, inter-laboratory comparisons should be  
242 organized, especially in case of multicenter PK studies.

243 *Collection of covariates affecting dose-exposure relationships*

244 In order to comprehensively understand and describe dose-exposure relationships, collection  
245 of accurate dosing information, demographic, clinical and para-clinical data is mandatory.

246 Regarding dosing information, galenic forms and routes of administration are important data.  
247 It is common practice in the setting of an ICU, where the patient is unable to swallow solid  
248 oral dosage forms, to administer drugs through enteral feeding tubes. In this situation, the  
249 administration of crushed tablets in the feeding tube may have an impact on bioavailability,  
250 which may alter the dosing-exposure relationship of the studied drug. This has been  
251 demonstrated in the HIV setting where crushing tablets of LPV have led to a 45% decrease in  
252 AUC (Best et al., 2011). Surprisingly, crushing tablet does not appear to have a significant  
253 impact on the oral bioavailability of HCQ (Sanofi, personal communication).

254 The dosing regimen may include a loading dose that is particularly important in view of more  
255 rapidly achieving effective concentrations. This point is critical for HCQ due to its very long  
256 half-life (Lê et al., 2020; Tett et al., 1989). A loading dose has also been suggested for LPV  
257 (Smith et al., 2020) and is required for remdesivir (European Medicines Agency. Summary on  
258 remdesivir compassionate use. April 2020).

259 Knowledge of co-administered drugs is likewise of primary importance, particularly in the  
260 context of ICU, where many medications are involved or when complications such as  
261 secondary infections are present, requiring co-administration of antibacterials and antifungals  
262 (Sanders et al., 2020). Co-medications are also frequent in patients particularly at risk for  
263 severe COVID-19, i.e. chronic disease patients such as obese and/or diabetic patients. Indeed,  
264 drug-drug interactions may occur at each step of the ADME process, leading to altered  
265 pharmacokinetics and, possibly, in increased variability of drug exposure. Divalent cations,  
266 such as calcium or magnesium, may interfere with the absorption of chloroquine (McElnay et  
267 al., 1982), thereby reducing its bioavailability. Similarly, LPV and HCQ, which undergo CYP

268 mediated metabolism (Liverpool HIV group. Liverpool COVID-19 Interactions.  
269 <https://www.covid19-druginteractions.org/>, 2020), could be victims of drug-drug interactions  
270 affecting both bioavailability and clearance. Although remdesivir is also a substrate for CYP  
271 isoenzymes *in vitro*, its metabolism is likely to be predominantly mediated by hydrolase  
272 activity (Liverpool HIV group. Liverpool COVID-19 Interactions. [https://www.covid19-  
druginteractions.org/](https://www.covid19-<br/>273 druginteractions.org/), 2020), but this does not stave off inter- nor intra-patient variability.

274 Anthropometric characteristics, which are currently involved in PK variability, should be  
275 collected as well. Body weight has been described as a significant covariate of HCQ clearance  
276 in Japanese patients suffering from systemic lupus erythematosus (Morita et al., 2016).  
277 Whether this relationship is valid in COVID-19 patients requires confirmation.

278 The use of specific organ support techniques (Zhang et al., 2020) such as renal replacement  
279 therapy (hemodialysis, hemofiltration, hemodiafiltration) or ventilation support (high-flow  
280 oxygen therapy, noninvasive ventilation, invasive mechanical ventilation and extracorporeal  
281 membrane oxygenation, ECMO) should be reported in order to assess their impact on drug  
282 exposure. A significant impact of hemodialysis on the pharmacokinetics of HCQ (Tett et al.,  
283 1989) and LPV (Gupta et al., 2008) is unlikely but requires confirmation since steady-state  
284 conditions are not achieved in COVID-19 patients. An impact of ECMO on chloroquine  
285 pharmacokinetics has been described (Bagate et al., 2017) but no convincing data exist yet for  
286 LPV (Ghazi Suliman et al., 2017). However, a significant impact of ECMO should be  
287 considered since several studies have shown altered PK profiles in this situation (Ha and Sieg,  
288 2017). These data need to be confirmed in COVID-19 patients, especially considering  
289 differences in steady-state attainment.

290 Importantly, severe COVID-19 is associated with a systemic hyper-inflammation state, the so-  
291 called cytokine storm, which is associated with highly elevated C-reactive protein (CRP)

292 levels, hyperferritinaemia and increased cytokine levels (IL-1 $\beta$ , IL-2, IL-6, IL-17, IL-8, TNF  
293 and CCL2) (McGonagle et al., 2020). The impact of inflammation on the pharmacokinetics of  
294 drugs has already been highlighted. For example, several studies have reported a positive  
295 association between CRP levels and voriconazole or tacrolimus concentrations (Bonneville et  
296 al., 2020; Gautier-Veyret et al., 2019). The extent of increase in voriconazole concentration  
297 could be explained by downregulation of CYP isoenzymes by inflammatory stimuli leading to  
298 reduced metabolism (Morgan, 2009). Impact may also occur through altered expression of  
299 membrane transporters (Seifert et al., 2017). Preliminary data suggest a major decrease of  
300 LPV clearance in COVID-19 patients, highlighting the putative role of inflammation in these  
301 PK alterations.

#### 302 *Development of population PK and PK-PD models*

303 Population approaches, which rely on PK-PD modeling, appear particularly appealing in this  
304 situation because these models can handle sparse data originating from different sources  
305 (ICU, non-ICU, dialysis patients) and different dosing regimens. Further, covariates as  
306 described above can be included in these population models to identify PK and  
307 pharmacodynamic (PD) variability factors. Finally, population-PK and PK-PD models have  
308 proven useful in the area of infectious diseases, providing a valuable tool to explore and  
309 predict efficient dosing regimens (Jumah et al., 2018). However, we believe that the  
310 development of population PK models specifically dedicated to acute COVID-19 patients is  
311 urgently needed due to major physiopathological differences with chronically ill HIV, RA and  
312 SEL patients. For that purpose, a collaborative multicenter study within clinical centers  
313 involved in clinical trials with these drugs may enable collection of the amount of data  
314 necessary to develop such a PK model. Such a collaborative project is ongoing within our  
315 groups.

316 Current dosing regimens proposed for these repurposed drugs are empirical since they have  
317 not been specifically developed for COVID-19 but rather for HIV, malaria and chronic  
318 inflammatory diseases. In order to develop more efficient dosing regimens, we also need  
319 reliable PD data to relate the concentration at the site of infection to viral sensitivity through  
320 the development of PK-PD models. Viral sensitivity could be determined through the  
321 measurement of EC50 or EC90 either in presence or in absence of human serum. Addition of  
322 human serum enables representation of the impact of drug protein binding on drug potency.  
323 EC50 is available for HCQ (Liu et al., 2020; Yao et al., 2020), LPV (Choy et al., 2020),  
324 favipiravir (Eloy et al., 2020), remdesivir (Choy et al., 2020) and other drugs such as  
325 ivermectin (Table II). But, as observed in Table II, translation into effective therapies may be  
326 challenging due to unfavorable *in vivo* PK properties. For example, ivermectin, total (bound  
327 and unbound) plasma concentrations are >45 times lower than the *in vitro* EC50. Since  
328 ivermectin is highly bound to plasma protein and its accumulation into human lung unknown  
329 (Schmith et al., 2020), the likelihood for ivermectin to reach IC50 at the site of action after the  
330 approved dose is low. The large variability reported in EC50 values between studies, mainly  
331 explained by differences in experimental conditions or mechanism of action, may also  
332 contribute to the difficulty of determining the accurate target concentration *in vivo*. For  
333 example, with HCQ, we observed high variability between EC50 values (i.e. for HCQ: from  
334  $0.72 \mu\text{M} \approx 0.24 \mu\text{g/mL}$  to more than  $15 \mu\text{M} \approx 5 \mu\text{g/mL}$ ) depending on MOIs, incubation  
335 duration, presence/absence of human serum, etc..., which may be of PK relevance for a drug  
336 presenting such a narrow therapeutic index. As reported in Figure 1, HCQ median plasma  
337 concentrations could be 1.5 to 15 times lower than the *in vitro* EC50 depending on the scheme  
338 of administration (and EC50 values. Moreover, the choice of experimental cells (Vero E6  
339 cells or pulmonary epithelial cells) may be crucial for such respiratory viruses, although no  
340 consensus has yet arisen, and extrapolations from other viruses appear speculative (Smith et

341 al., 2020). Finally, regarding the lack of specificity/sensitivity of the current virological  
342 marker (i.e viral load in the upper respiratory tract) to assess antiviral activity, the  
343 combination of multiple PD parameters could be of interest. The relationships between viral  
344 load and clinically relevant endpoints is mostly unknown. Indeed, many clinical endpoints  
345 could be considered: mortality, recovery, hospital discharge, respiratory failure, need for  
346 oxygenation or mechanical ventilation, time-to-intubation, hospitalization, duration of  
347 hospital-stay, ICU admission, time-to-improvement, severity scores (SOFA), etc. Selecting  
348 the best clinically relevant endpoint may depend upon several factors such as its clinical  
349 relevance, its measurement's reliability, disease severity and statistical considerations.

350 In order to assess drug penetration to the site of action, determination of drug concentration in  
351 bronchoalveolar lavage could be proposed as a surrogate for lung concentrations. Urea or  
352 albumin should be used as a marker of dilution to determine the volume of epithelial lining  
353 fluid recovered and samples should be preferably collected at multiple time points throughout  
354 the dosing interval (Rodvold et al., 2011). To our knowledge, corresponding data for COVID-  
355 19 treatment candidates are scarce. A case study in a single HIV patient (Atzori et al., 2003)  
356 reported significant LPV concentration in BAL at steady-state. ELF and total plasma  
357 concentrations were 14.4 and 8.1 µg/mL, respectively. The corresponding ratio of ELF over  
358 total plasma concentrations was 1.8, suggesting an accumulation of LPV in ELF requiring  
359 confirmation in COVID-19 patients. Data of the same order of magnitude but with less  
360 accumulation were also reported by Boffito et al (Boffito et al., 2002).

361

## 362 *Conclusion*

363 Available PK and PK-PD studies suffer from severe limitations leading to unreliable  
364 conclusions, especially in term of dosing optimization. At this time, there is still no high-



365 quality evidence to support the use of these repurposed drugs for the treatment of COVID-19.  
366 Therefore, implementation of well-designed PK and PD studies specifically targeted to  
367 COVID-19 patients is urgently needed in order to increase our comprehension of the dose-  
368 exposure-effect relationships of the repurposed drugs. Without these data, efficient evaluation  
369 and development of effective dosing regimens will remain difficult. Other scientific societies  
370 (Baker et al., 2020) and organizations (Hartman et al., 2020; Rayner et al., 2020) have also  
371 recently issued call to action for the appropriate application of clinical pharmacology  
372 principles in the search for COVID-19 treatments. Further, to accelerate the production of up-  
373 to-date PK and PD data and the development of meaningful PK and PK-PD models, we also  
374 call for multi-institutional collaborative work and involvement of clinical pharmacologists in  
375 multidisciplinary research consortia.

376

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579 Table I : Pharmacological issues relative to COVID-19 infection in clinical trials : 18 studies found for: **Pharmacokinetic | COVID-19**

580

Clinical trial Identifier	Official Title	Primary outcome	Experimental drug	Pharmacological
NCT04345614	A Randomized Controlled Open-Label Study of CM4620 Injectable Emulsion in Patients with Severe COVID-19 Pneumonia	Safety, efficacy, and the PK profile of CM4620-IE in patients with severe COVID-19 pneumonia.	CM4620-Injectable Emulsion	M4620-IE serum concentration
NCT04357613	A RANDOMIZED NON-COMPARATIVE PHASE 2 PILOT STUDY TESTING THE VALUE OF IMATINIB MESYLATE AS AN EARLY TREATMENT OF COVID-19 DISEASE IN AGED HOSPITALIZED PATIENTS.	To evaluate the benefit of early imatinib therapy to prevent severe COVID-19 disease in hospitalized aged patients. [Time Frame: 30 days]	Imatinib 800mg/d during 14days	To evaluate plasma levels of imatinib [Time Frame: 14 days]  Imatinib trough level
NCT04346628	A Phase 2 Randomized, Open Label Study of Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild COVID-19	Time until cessation of oral shedding of SARS-CoV-2 virus [ Time Frame: Up to 28 days ]	Favipiravir administered orally, 1800 mg on the first dose (day 1) followed by 800 mg twice daily for the next 9 days (days 2-10).	Cmax of favipiravir [Time Frame: Days 1 and 10 (samples taken 30 minutes prior to and 1 hour following favipiravir administration)]
NCT04358549	Open Label, Randomized, Controlled Phase 2 Proof-of-Concept Study of the Use of Favipiravir v. Standard of Care in Hospitalized Subjects With COVID-19	Time to viral clearance [Time Frame: Day 29]; To determine the effect of favipiravir + SOC v. SOC on viral clearance of COVID-19 as measured by nasopharyngeal and oropharyngeal sampling	Day 1: favipiravir 1800 mg BID plus Standard of Care (SOC) Days 2-14: 1000 mg BID plus SOC. For subjects with Child-Pugh A liver impairment: Days 2-14: 800 mg BID plus SOC	Plasma PK of favipiravir
NCT03891420	A Phase 1b Double-blind, Placebo-controlled, Dose-ranging Study to Evaluate the Safety, Pharmacokinetics , and Anti-viral Effects of Galidesivir Administered Via	Number of subjects with 1-treatment emergent adverse events and serious adverse	Galidesivir IV infusion	Exposure of galidesivir as measured by plasma concentrations

	Intravenous Infusion to Subjects With Yellow Fever or COVID-19	events  2- change in laboratory parameters		
NCT03648372	An Open Label, Dose-Escalation, Phase I Study to Evaluate the Safety, Tolerability and Pharmacokinetics of TAK-981 in Adult Patients With Advanced or Metastatic Solid Tumors or Relapsed/Refractory Hematologic Malignancies and in a Subset With Coronavirus Disease 2019	COVID-19 proof of concept: Once the Safety Lead-in is complete and a TAK-981 dose and regimen is selected by the Safety Monitoring Committee (SMC), the randomized COVID-19 proof of concept will begin with participants randomized to Arm A: COVID-19 standard of care (SOC), or Arm B COVID-19 SOC + TAK-981.	TAK-981 Intravenous infusion	TAK-981 COVID-19 safety lead-in: TAK-981, intravenously, administered as 60 minute-infusion, once on Days 1 and 4. The starting dose of TAK-981 will be 60 milligram (mg).
NCT04371640	A Randomized, Double-Blinded, Placebo-Controlled Trial Evaluating the Virological Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Sirolimus Adjuvant Therapy in Patients With COVID-19	Change in SARS-COV-2 viral burden from baseline to day 7 of treatment [Time Frame: Baseline, and days 1, 2, 3, 4, 5, 6, & 7 post-dose for all patients]  SARS-COV-2 viral burden will be quantified for both arms using a qRT-PCR	Sirolimus + standard medical care Day 1: 10mg Days 2-7: 5mg  Intervention: Drug: Sirolimus 1 MG/ML	PK of sirolimus
NCT04363736	A Phase-II, Open-Label, Randomized, Multicenter Study to Investigate the Pharmacodynamics, Pharmacokinetics, Safety, and Efficacy of 8 mg/kg or 4mg/kg Intravenous Tocilizumab in Patients With Moderate to Severe COVID-19 Pneumonia	Concentration of C-Reactive Protein (CRP) [Time Frame: Day 7]	Participants will receive intravenous (IV) tocilizumab (TCZ) at a dose of 8 mg/kg vs 4 mg/kg in addition to standard-of-care treatment.	Concentration of C-Reactive Protein (CRP) as surrogate marker of TCZ PK
NCT04320615	A Randomized, Double-Blind, Placebo-	Clinical Status Assessed Using a	Participants will receive 1	Serum Concentration of TCZ



	Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	7-Category Ordinal Scale [ Time Frame: Day 28 ]	intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose may be given if clinical symptoms worsen or show no improvement.	[Time Frame: Up to 60 days]
NCT04158648	A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Emicizumab in Patients With Mild or Moderate Hemophilia A Without FVIII Inhibitors	17 primary outcomes	4 loading doses of emicizumab 3 mg/kg will be administered subcutaneously once a week (QW) for 4 weeks followed by participant's preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W).	Plasma Trough Concentration (C <sub>trough</sub> ) of Emicizumab Over Time [Time Frame: Pre-dose at Weeks 1, 2, 3, 4, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, and 49, and every 12 weeks thereafter until study completion/discontinuation (up to approximately 30 months)]
NCT04278404	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs	Usual PK parameters	Aminocaproic acid, Amiodarone, Bosentan, Budesonide, Cefdinir, Cefepime, Ceftazidime, Clindamycin, Clobazam, Dexamethasone, Dexmedetomidine, Dextroamphetamine/Amphetamine-Immediate Release, Fosfomycin Furosemide, Gabapentin Guanfacine, Hydrocortisone Labetalol, Meropenem, Metformin Milrinone, Nalbuphine, Nicardipine, Nifedipine, Oseltamivir, Oxycodone, Risperidone, Sertraline, Sevelamer Carbonate / Sevelamer,	The POPO2 study is collecting bodily fluid samples (i.e., whole blood, effluent samples) of children prescribed the following drugs of interest per standard of care:  The prescribing of drugs to children is not part of this protocol. Participants will receive DOIs as prescribed by their treating provider.

			<p>Hydrochloride, Spironolactone, Terbutaline, Tranexamic acid</p> <p>Voriconazole, Zolpidem</p> <p>Dextroamphetamine /Amphetamine - Extended Release, Azithromycin</p> <p>Chloroquine, Hydroxychloroquine, Lopinavir/Ritonavir, Ribavirin, Tocilizumab</p>	
NCT04392219	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	<p>Safety and Tolerability of Single Ascending Dose (SAD) of EIDD-2801 (Part 1) and Multiple Ascending Dose (MAD) of EIDD-2801 (Part 3): Adverse Events [ Time Frame: From screening through study completion, up to 15 days ]</p> <p>Number and severity of treatment emergent adverse events</p>	<p>Part 1: Subjects will be randomized to receive a single oral dose of EIDD-2801 or Placebo.</p> <p>Part 3: Subjects will be randomized to receive twice daily dosing either EIDD-2801 or Placebo.</p>	<p>Pharmacokinetics (PK) of EIDD-2801 when given as Single Doses (Part 2): Maximum observed concentration Cmax [ Time Frame: Day 1 through Day 18 ]</p> <p>Multiple pharmacokinetic variables of EIDD-2801 will be assessed and may include, but are not limited to: Maximum observed concentration Cmax</p>
NCT04346199	A Phase 2, Open Label, Randomized Study of the Efficacy and Safety of Acalabrutinib With Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized With COVID-19	Subject alive and free of respiratory failure [ Time Frame: Day 14 ]	Acalabrutinib- administered orally	Plasma PK parameters of acalabrutinib and its active metabolite ACP- 5862 [ Time Frame: 28 days after last dose ]
NCT04380688	A Phase 2, Open Label, Randomized Study of the Efficacy and Safety of Acalabrutinib With Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized With COVID-19	<p>Occurrence of Adverse Events and Serious Adverse Events [Time Frame: 28 days after last dose]</p> <p>Subject alive and free of</p>	Acalabrutinib- administered orally	Plasma PK parameters of acalabrutinib and its active metabolite ACP- 5862 [Time Frame: 28 days after last dose]

		respiratory failure [Time Frame: Day 14]		
NCT04350736	A Phase 1, Double-blind, Randomized, Placebo-controlled, Sponsor-open, SAD and MAD Study in Healthy Subjects to Evaluate the Safety, Tolerability, and PK of Inhaled TD-0903, a Potential Treatment for ALI Associated With COVID-19	Safety and Tolerability of MAD of TD-0903: Adverse Events [ Time Frame: Day 1 to Day 14 ]  Number and severity of treatment emergent adverse events	TD-0903  Study drug to be administered by inhalation	Plasma PK parameters of SAD and MAD TD-0903
NCT04369469	A Phase 3 Open-label, Randomized, Controlled Study to Evaluate the Efficacy and Safety of Intravenously Administered Ravulizumab Compared With Best Supportive Care in Patients With COVID-19 Severe Pneumonia, Acute Lung Injury, or Acute Respiratory Distress Syndrome	Survival (based on all-cause mortality) at Day 29 [ Time Frame: Baseline, Day 29 ]	Weight-based doses of ravulizumab will be administered intravenously on Days 1, 5, 10, and 15.  Other Names:  Ultomiris  ALXN1210	PK parameters of ravulizumab
NCT04379271	A Prospective, Multi-Center, Randomized, Placebo-Controlled, Double-Blinded Study to Evaluate the Efficacy, Safety and Tolerability of IMU-838 as Addition to Investigator's Choice of Standard of Care Therapy, in Patients With Coronavirus Disease 19	Proportion of patients without any need for INV until end-of-study (EoS) [ Time Frame: Throughout the Study (Day 0 to Day 28) ]  Clinical	twice-daily (BID) oral 22.5 mg IMU-838 (45 mg/day + SoC)	Morning trough plasma levels of IMU-838 on Days 0, 1, 2, 3, 6, 14, and 28 [ Time Frame: on Days 0, 1, 2, 3, 6, 14, and 28 ]
NCT04315948	Multi-centre, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults	Percentage of subjects reporting each severity rating on a 7-point ordinal scale [ Time Frame: Day 15 ]  a-Not hospitalized, no limitations on activities  b-Not hospitalized, limitation on	Remdesivir will be administered as a 200 mg intravenous loading dose on Day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalization up to a 10 days total course.	Plasma concentration of lopinavir [ Time Frame: Days 1, 3, 5, 8 and 11 ]  On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second

		<p>activities;</p> <p>c-Hospitalized, not requiring supplemental oxygen;</p> <p>d-Hospitalized, requiring supplemental oxygen;</p> <p>e-Hospitalized, on non-invasive ventilation or high flow oxygen devices;</p> <p>f-Hospitalized, on invasive mechanical ventilation or ECMO;</p> <p>g-Death.</p>	<p>Lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir) will be administered every 12 h for 14 days in tablet form. For patients who are unable to take medications by mouth, the lopinavir/ritonavir (400 lopinavir mg/100 mg ritonavir) will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube.</p> <p>Interferon <math>\beta</math>1a will be administered subcutaneously at the dose of 44 <math>\mu</math>g for a total of 3 doses in 6 days (day 1, day 3, day 6).</p> <p>Hydroxychloroquine will be administered orally as a loading dose of 400 mg twice daily for one day followed by 400 mg once daily for 9 days. The loading dose of hydroxychloroquine through a nasogastric tube will be increased to 600 mg twice a day for one day, followed by a maintenance dose of 400 mg once a day for 9 days</p>	<p>administration (trough at H12)</p> <p>On Days 3, 5, 8 and 11, trough plasma concentration (before dose administration) while hospitalized</p> <p>Plasma concentration of hydroxychloroquine [ Time Frame: Days 1, 3, 5, 8 and 11 ]</p> <p>On Day 1, plasma concentration 4 hours after the first administration (peak), and before the second administration (trough at H12)</p> <p>On Days 3, 5, 8 and 11, trough plasma concentration (before dose administration) while hospitalized</p>
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584 Table II: available EC<sub>50</sub> against SARS-CoV-2 and corresponding total plasma concentrations  
 585 obtained in human

Repurposed drug	<i>In vitro</i> antiviral activity against SARS-CoV-2	Plasma total concentrations in human (SARS-CoV-2 infected patients)	Plasma total concentrations in human (others populations)
Lopinavir	EC <sub>50</sub> = 26.63 μM (16.75 μg/mL)(Choy et al., 2020)  EC <sub>50</sub> = 15.27 μM (9.60 μg/mL)(Jeon et al., 2020)	400/100 mg BID: C <sub>trough</sub> [11.4 – 30.8 μg/mL]  400/100 mg QD: C <sub>trough</sub> [8.7 – 18.3 μg/mL](Gregoire et al., 2020)	
Remdesivir	EC <sub>50</sub> = 0.77 μM (0.46 μg/mL)(Wang et al., 2020)  EC <sub>50</sub> = 23.15 μM (13.95 μg/mL)(Choy et al., 2020)  EC <sub>50</sub> = 8.24 μM (4.97 μg/mL)(Jeon et al., 2020)  EC <sub>50</sub> = 165 +/- 0.79 μM (99.43 μg/mL)(Touret et al., 2020)		<b>Healthy subjects</b>  100 mg QD for 5 to 10 days :  Mean (SD) GS-443902 C <sub>24</sub> in PBMCs = 10.2 (5.5) μM (Day 5) (European Medicines Agency. Summary on remdesivir compassionate use. April 2020)
Hydroxychloroquine	EC <sub>50</sub> = 0.72 μM (0.24 μg/mL)(Yao et al., 2020)  EC <sub>50</sub> = 4.51 μM (1.47 μg/mL)(Liu et al., 2020)  EC <sub>50</sub> = 4.17 μM (1.35 μg/mL)(Touret et al., 2020)	200mg TID MD without LD: C <sub>trough</sub> = 0.09 +/- 0.01 (H8 on day 2) to 0.19 +/- 0.06 (H8 on day 6) μg/mL  400mgx2 LD on day 1 followed by 400x1 MD: C <sub>trough</sub> = 0.09 +/- 0.12 (H12 on day 2) to 0.13 +/- 0.14 (H12 on day 6) μg/mL (Martin-Blondel et al., n.d.)	
Favipiravir	EC <sub>50</sub> = 9.4 μg/mL  EC <sub>50</sub> = 40-80 μg/mL(Eloy et al., 2020)  EC <sub>50</sub> > 100 μM (>15.71 μg/mL)(Choy et al., 2020)  EC <sub>50</sub> > 500 μM (>78.55 μg/mL)(Jeon et al., 2020)		<b>Ebola patients</b>  6000 mg on day 0 followed by 1200 mg BID for 9 days : Median (range) C <sub>trough</sub> = 46.1 (2.3 – 106.9) μg/mL on day 2 and 25.9 (0 – 173.2) μg/mL on day 4(Nguyen et al., 2017)
Ivermectin	EC <sub>50</sub> = 2 μM (1750 ng/mL)(Caly et al., 2020)		<b>Onchocerciasis patients</b>  Single dose of 150 μg/kg PO: C <sub>max</sub> = 38.2 +/- 5.8 ng/mL(Okonkwo et al., 1993)

586 \*Remdesivir is a prodrug rapidly converted to a circulating monophosphate nucleoside analog  
 587 (GS-441524) which inside cells undergoes rapid conversion to the pharmacologically active  
 588 analog of adenosine triphosphate (GS-443902) that inhibits viral RNA polymerases. LD =  
 589 loading dose, MD = maintenance dose.

590 Figure 1. Observed hydroxychloroquine plasma concentrations (median) after 3-5 days of  
591 treatment in patients treated for SARS-CoV-2 infection depending on the scheme of  
592 administration: 400mg QD after a loading dose of 400mgx2 on day 1 and 200mg TID without  
593 any loading dose (C. Solas, internal data from the Pharmacokinetics and Toxicology  
594 Laboratory). Solid line represent *in vitro* EC50 described against SARS-CoV-2 at T48h post  
595 incubation.

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