The antiviral remdesivir – an example of expedited approval procedures in the USA within the Covid-19 pandemic

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List of Abbreviations

AE	Adverse event
ACTT-1	Adaptive COVID-19 Treatment Trial 1
ACE2	Angiotensin-converting enzyme 2
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration time curve
BLA	Biologics license application
BTD	Breakthrough Therapy Designation
CC_{50} (or $CCIC_{50}$)	Median cellular cytotoxicity concentration
CDER	Center for Drug Evaluation and Research
CHC	Chronic hepatitis C
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximal plasma drug concentration
C_{min}	Minimal plasma drug concentration
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CTAP	Coronavirus Treatment Acceleration Program
CYP	Cytochrome P450
DAA	Direct-acting antiviral
DDI	Drug-drug interaction
E protein	Envelope protein
EBOV	Ebola virus
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ER	Endoplasmic reticulum
ERGIC	ER-to-Golgi intermediate compartment
EU	European Union
EUA	Emergency Use Authorization
EVD	Ebola virus disease
ExoN	Exoribonuclease
FDA	Food and Drug Administration
FIH	First-in-human
FTD	Fast-Track Designation
HAE	Human airway epithelial cells
HCV	Hepatitis C virus
HHS	Department of Health and Human Services
HIV	Human immunodeficiency virus
INR	International normalised ratio

ITT	Intention-to-treat
IP	Investigational product
IQ	Inhibitory quotient
IND	Investigational new drug application
IP	Investigational product
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
Mab	Monoclonal antibody
M protein	Membrane protein
MERS-CoV	Middle East respiratory syndrome coronavirus
MOA	Mechanism of action
NDA	New drug application
NHP	Non-human primates
NIAID	National Institute of Allergy and Infectious Diseases
NMP	Nucleoside monophosphate
nsps	Non-structural proteins
NRTI	Nucleoside reverse-transcriptase inhibitor
NtRTIs	Nucleotide reverse transcriptase inhibitors
NTP	Nucleoside triphosphate
PBMC	Peripheral blood mononuclear cells
PI	Prescribing information
PK	Pharmacokinetics
PMC	Post-marketing commitment
PMR	Post-marketing requirement
PPB	Plasma protein binding
PRIME	PRIority MEdicines
PT	Prothrombin time
RCT	Randomised controlled clinical trials
RBD	Receptor-binding domain
RDV	Remdesivir
RdRP	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
RRR	Recovery rate ratio
S protein	Spike protein
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBECD	Sulfobutylether-β-cyclodextrin sodium
SI	Selectivity (or therapeutic) index
SOC	Standard of care
SVR	Sustained virological response
ssRNA	Single-stranded RNA
T½	Elimination (or plasma) half-life
US	United States of America

WHO	World Health Organisation

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1. Introduction to Covid-19 and SARS-CoV-2

Over the last two decades three coronaviruses have caused large-scale outbreaks in the human population. These zoonotic pathogens include severe acute respiratory syndrome coronavirus (SARS-CoV; outbreak 2002–2003), Middle East respiratory syndrome coronavirus (MERS-CoV; outbreak 2012) and the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The latter has caused the coronavirus disease 2019 (COVID-19) pandemic and was first reported in Wuhan City/China on 31 December 2019. The World Health Organisation (WHO) declared COVID-19 as a pandemic on 11 March 2020. (1–4) As a new disease, COVID-19 did not have any clinically proven drugs. Therefore, there is intensive research worldwide on drugs for the treatment or prevention of COVID. (5)

Infections with these viruses can develop into severe, life-threatening respiratory pathologies. (6) The most common symptoms of COVID-19 are fever, cough, dyspnoea, chest pain, fatigue and myalgia, while decreased or loss of taste and olfactory perceptions have also been reported. Clinical severity ranges widely, from asymptomatic infection to critical illness. Risk factors for hospitalisation include, age > 65 years, hypertension, obesity, diabetes, cardiovascular disease, and chronic lung disease. (7–9)

2. SARS-CoV-2 properties, lifecycle and potential targets for antivirals

2.1 Morphology and genomic structure of SARS-CoV-2

Coronaviruses (CoVs) form the highly diverse family *Coronaviridae*, and are enveloped with a positive sense, single-stranded, RNA (+ssRNA). Within this family SARS-CoV-2, SARS-CoV and MERS-CoV belong to the *betacoronavirus*. SARS-CoV-2 shows 79% and 50% sequence identity with SARS-CoV and with MERS-CoV, respectively. (1,4,6,7,10)

The name “coronavirus” is derived from the crown-shape spike glycoprotein projecting from its surface (see *Fig. 1*). The spike (S) protein attaches to cellular receptors on the host cell and mediates viral entry. Host specificity is believed to be largely dependent upon variation in the S glycoprotein. (1,4,6,7,10)

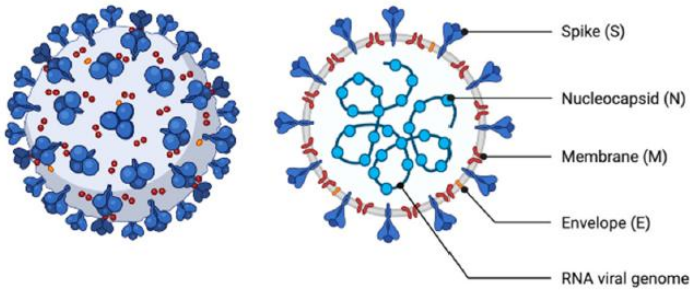

Fig. 1: Human corona virus structure[1]

The virus particle (virion), consists of the two basic components: genomic RNA and a protein capsid which are packaged to a nucleocapsid (N). The viruses consist of the following structural proteins: N, S, envelope (E) and membrane (M) proteins. These proteins are responsible for host infection, membrane fusion, viral assembly, morphogenesis and release of virions. The virions also contain non-structural proteins which facilitate viral replication and transcription. (1,4,6,7,10)

The S proteins are clove-shaped, trimeric transmembrane proteins. One domain of S proteins consists of the S1 subunit, containing a receptor-binding domain (RBD). The initial step of viral infection is the host-cell receptor recognition and receptor attachment by the RBD. Another domain is the membrane-fusion subunit (S2). (1,4,6,7,10)

2.2 Life cycle of SARS-CoV-2

Since the complete mechanisms of SARS-CoV-2 have not been thoroughly studied yet, the replication of SARS-CoV-2 can be explained based on SARS-CoV and MERS-CoV models. During the intracellular life cycle (*Fig. 3*), coronaviruses express and replicate their genomic RNA to produce copies that are incorporated into newly produced viral particles. (1,2,4,6,7,11,10,12)

Upon viral transmission, mostly via droplet transmission, the life cycle of SARS-CoV-2 is initiated. Viral entry (*Fig. **2***) into the host cell is a multistep process in which SARS-CoV-2 utilizes the RBD of the S protein to recognize angiotensin-converting enzyme 2 (ACE2) receptors on the human cells leading to plasma membrane fusion. ACE2 is expressed mainly in the respiratory tract, heart and nasal mucosa. A second pathway of viral uptake

[1] Reference: (4)

is also promoted by host factors (such as the transmembrane serine protease 2, TMPRSS2) that support viral uptake via endosomes and fusion at the cellular membrane. (1,2,4,6,7,11,10,12)

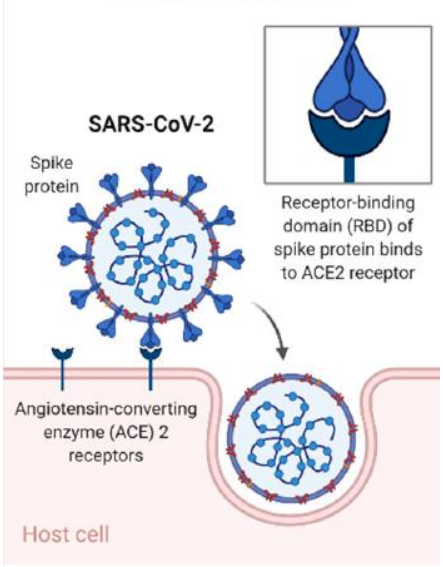

Fig. 2: Viral entry mechanism of SARS-CoV-2
SARS-CoV-2 first binds to host-cell ACE2 receptors and then penetrates into the target cell. (4)

Following entry, the envelope is peeled off (*Fig. 3*). The released and uncoated viral RNA is subject to immediate translation of the replicase gene. The resulting polyproteins pp1a and pp1ab help hijacking host ribosomes for the viral translation process. During translation they are processed into the non-structural proteins (nsps) that form the complex for viral RNA replication and transcription viral mRNAs. The nsp12 protein forms a replicase-transcriptase complex called RNA-dependent RNA polymerase (RdRP). RdRP produces via reverse transcription a complementary negative-sense RNA using the original positive RNA as a template. This negative-strand RNA is then transcribed by viral replicase to new positive RNA molecules that are replicated and translated to form the new virions. (1,2,4,6,7,11,10,12)

The translated viral structural proteins require post-translational modification for assembly and budding of the enveloped virus (*Fig. 3*). The replicated RNA forms a structural protein complex including S, E, M and N proteins. The S, E, and M proteins translocate into the endoplasmic reticulum (ER). The positive sense RNA and N protein form the nucleocapsid. The nucleocapsid combines with S, E and M proteins and transits through the ER-to-Golgi intermediate compartment (ERGIC), where newly produced genomic RNA

results in budding into secretory vesicular compartments. Finally, mature viruses are released from the infected cell by exocytosis. (1,2,4,6,7,11,10,12)

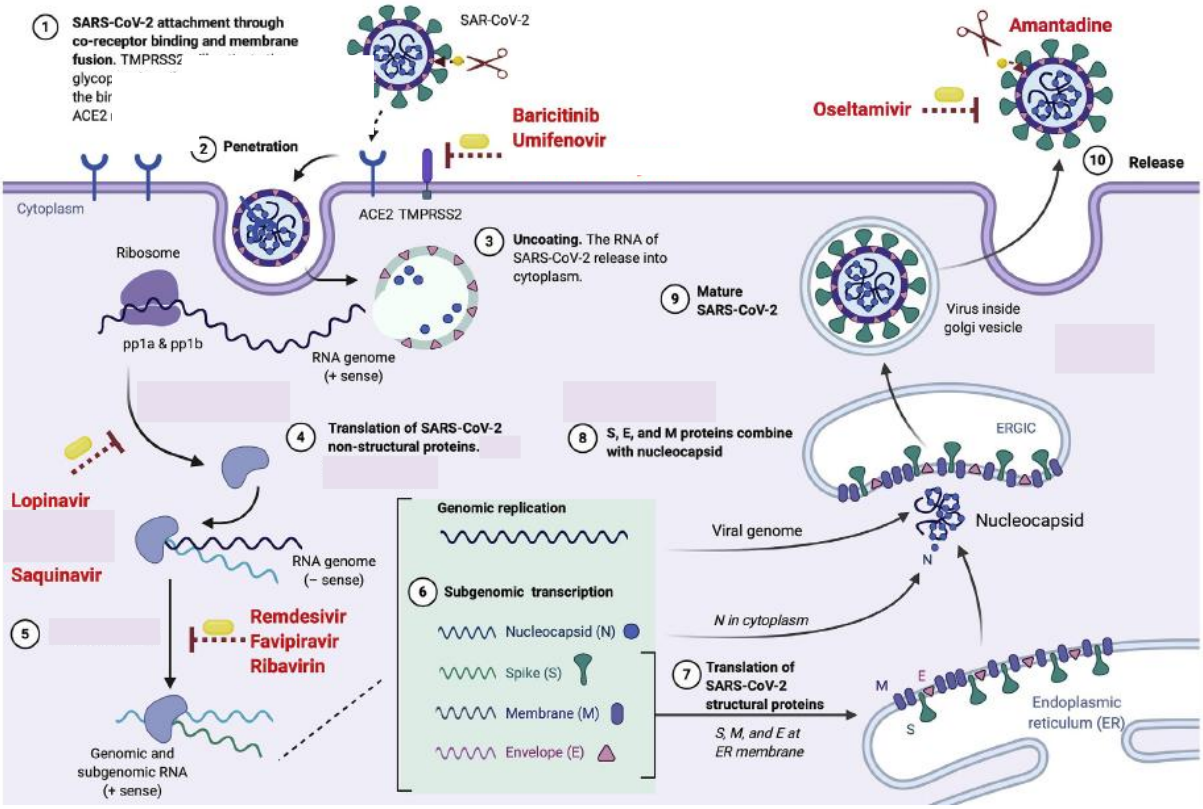

Fig. 3: Life cycle of SARS-CoV-2 and potential antiviral targets
+ sense RNA: positive sense ss (single stranded) RNA; - sense RNA: negative sense ss RNA. For a description of life cycle steps 1) to 10) see above (*section 2.2* ***Life cycle of SARS-CoV-2***). The possible antiviral drug targets are described below (*section 2.3* ***Characteristics of antivirals and their potential targets in the SARS-CoV-2 life cycle***). Figure modified according to (7).

2.3 Characteristics of antivirals and their potential targets in the SARS-CoV-2 life cycle

Many antiviral and immunological treatments are being investigated for the treatment of COVID-19. Antiviral drugs are believed to be useful especially during the early stage of the disease when active viral replication prevails. Immunomodulating agents are generally being evaluated for use during the pro-inflammatory stage that presents later in the course of infection. This stage is believed to be mediated by cytokines, such as interleukin 6. (4,7,13–15)

2.3.1 Characteristics of antivirals

Below potential targets for antivirals are discussed. What is an antiviral therapy? No definition for antiviral drugs could be found. But the requirements for antiviral agents can be

identified: they must have *inhibitory effects on virus-specific events*, including attachment to the cell, uncoating of the genome of the virus, or on virus-directed synthesis of the viral nucleic acids and/or proteins. The inhibitory effect is also the FDA's requirement for an antiviral. If drugs that have not been tested for antiviral effects, those drugs should not be regarded as antivirals. Therefore, FDA does not consider drugs, such as chloroquine/hydroxychloroquine, as antivirals.

Only antiviral drugs are considered in this thesis. They are discussed in detail on the example of remdesivir. Non-antiviral drugs against SARS-CoV-2 infection, such as the FDA-approved anti-malarial drug chloroquine and hydroxychloroquine, are therefore not discussed. (4,7,13–17)

2.3.2 Potential targets of antivirals in the SARS-COV-2 life cycle

Several antiviral drugs are being repurposed (synonym: repositioned) for COVID-19 treatments. Repurposing is the investigation of approved drugs or drugs that have been under clinical development for other diseases for the treatment of new diseases. The principal target of antiviral drugs is to block the viral life cycle. The following sections describe the possible mechanisms of inhibiting the SARS-COV-2 life cycle at different stages (4,7,13–17)

2.3.2.1 Prevention of viral entry into the host cell

Fusion inhibitors prevent virus-mediated membrane fusion of viral entry into the host cells (*Fig. 3*). This seems to be achieved by modifying the physicochemical properties of the host cell membrane by influencing the negatively charged phospholipids. A representative is baricitinib. (7,11)

2.3.2.2 Blockage of viral proteases by protease inhibitors

Protease inhibitors are best known as treatment against human immunodeficiency virus (HIV) infection as inhibitors of HIV-1 protease. Protease inhibitors, such as lopinavir and ritonavir, have the potential also to target SARS-CoV-2 proteases (*Fig. 3*). Protease inhibi-

tors bind competitively to the substrate site of the viral protease, thereby preventing virus replication.

The combination of lopinavir and ritonavir was demonstrated to inhibit the main protease (Mpro) of SARS-CoV-2. Mpro represents an ideal antiviral target as its function is essential for viral replication for viral replication, transcription and maturation. Lopinavir has to be co-administered in a fixed-dose combination with ritonavir because of lopinavir's extensive hepatic metabolism and thus low oral bioavailability. Ritonavir acts as a booster by inhibiting the metabolic inactivation of lopinavir. (4,14)

2.3.2.3 RNA-dependent RNA polymerase (reverse transcription) inhibitors

Another strategy against SARS-CoV-2 infection involves targeting the reverse transcription by blocking RdRp and thus preventing viral replication (*Fig. 3*). Since the structure of SARS-CoV-2 RdRp is similar to that of other positive sense RNA viruses and some catalytic amino acid residues in the active site are conserved in most viral polymerases, this polymerase is an effective target of broad-spectrum direct-acting antivirals (DAAs). For example, nucleoside reverse-transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) of the HIV and hepatitis C virus (HCV) reverse transcriptase are the cornerstone of treatments to control HIV and HCV infections. Thus, NRTIs and NtRTIs used for the treatment of other viral infections have been repurposed for COVID-19. NRTIs include emtricitabine and lamivudine. Remdesivir and favipiravir are NtRTIs. Remdesivir is described in detail from *section 4* and following. (7,18–20)

2.3.2.4 Neuraminidase inhibitors

The neuraminidase inhibitor oseltamivir is effective in preventing influenza. Neuraminidase is expressed on the viral surface and supports the release of new virions from infected cells. Neuraminidase inhibitors are not expected to be effective against COVID-19 mainly because neuraminidase has not been found in SARS-CoV-2. (2,7)

2.3.2.5 M2 ion-channel protein blockers

The M2 ion-channel protein is located on the viral envelope and is essential in maintaining pH across the envelope. This is critical during cell entry of host cells. The M2 ion-

channel protein is also a target against influenza viruses. Amantadine is an example for an M2 ion-channel protein inhibitor. It was shown that amantadine was able to block the protein-membrane channel activity of SARS-CoV. (7)

3. Regulatory pathways, guidance and recommendations for the development of antiviral drugs in the USA and the EU

3.1 USA: Regulatory pathways, guidance and recommendations for the development of antiviral drugs, including specific programs during the COVD-19 pandemic

3.1.1 FDA guidance on antiviral product development – conducting and submitting virology studies to the agency

The "Guidance for Industry: Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency" was published 2006 and is still valid. (21)

This guidance has been further specified as guidance for the development of antiviral drugs for different viruses, e.g., the guidance concerning HIV-1 ("Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment") or HCV ("Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment"). (22,23)

The principal FDA guidance of general antiviral product development (21) contains non-binding recommendations[2] as generally applicable for all FDA guidance for industry. The guidance does not only cover small (chemical) molecules but also biological products (e.g., monoclonal antibodies). Its purpose is to assist sponsors in the development of antiviral drugs and biological products from the initial pre-IND[3] (investigational new drug application) through the new drug application (NDA) and post-marketing stages. It specifies what nonclinical and clinical virology studies are relevant to the development and necessary to support the submission of an IND, NDA, or biologics license application (BLA) for the approval of an antiviral drug. This guidance focuses on nonclinical and clinical virology study reports and makes recommendations for collecting resistance data.

[2] Non-binding recommendations are generally applicable for all FDA guidance for industry.
[3] Pre-IND: is an abbreviated IND format. (21)

Nonclinical virology studies (see *section 3.1.1.1 Nonclinical virology studies*) are a key focus of this guidance. Because nonclinical *in vitro* virology studies can provide useful information for the design of *in vivo* studies it is recommended to conduct them before the initiation of phase I clinical studies. (21)

3.1.1.1 Nonclinical virology studies

a) Mechanism of action studies

Antivirals can act directly to inhibit a virus by targeting a specific viral-encoded function (DAA) or act *indirectly* (induction of host cell response). The objectives of mechanism of action (MOA) studies are to demonstrate the investigational product's (IP) ability to inhibit a virus-specific function (e.g., viral replication) and identify the target site (e.g., viral replicase). Data that demonstrate the MOA include inhibition of enzymatic activity. A characterised MOA is useful in designing studies to assess the development of resistance. The specificity of the antiviral IP should be demonstrated for the viral target over host proteins, especially when a viral enzyme has a host cell counterpart. (21)

b) Antiviral activity

Antiviral activity in vitro

For human viruses with cell culture systems in which the virus can undergo a complete virus life cycle the guidance recommends to document that the IP and/or its metabolites shows specific and quantifiable antiviral activity *in vitro* before initiating tests in humans. The objective of these data is to support clinical testing in humans by providing clear evidence of antiviral effects at drug concentrations that can be achieved *in vivo* with acceptable risk-benefit. Furthermore, the selection of appropriate dose ranges in early clinical trials can be substantiated by *in vitro* antiviral activity and cytotoxicity assessments using relevant cell types and virus isolates. (21)

Antiviral activity studies recommended to support the development of the IP include:

- Assessing specific antiviral activity of the IP against a broad range of clinical and laboratory viral isolates, such as different genotypes. This is due to viral genetic variation.

- Evaluating the antiviral activity of the IP against mutant viruses that are resistant to drugs with the same viral target as the IP as well as a sample of viruses resistant to other approved products for the same indication. (21)

The antiviral activity should be determined by using a quantitative assay to measure virus replication in the presence of increasing drug concentrations compared to replication in the absence of the drug. By this the effective drug concentration can be determined *in vivo* or *in vitro* at which virus replication is inhibited by 50%:

- EC_{50}: plasma concentration required for obtaining 50% of a maximum effect *in vivo* (cell-based assays);
- IC_{50}: half maximal inhibitory concentration *in vitro* (biochemical or subcellular assays).

The EC_{50} or IC_{50} is a measure of resistance. (21)

Antiviral activity in vitro in the presence of serum proteins

As serum proteins can bind to many products and thus interfere with a product's antiviral activity it is recommended to determine the protein binding of the IP, e.g., to human serum albumin. (21)

Inhibitory quotient

In order to assess the dose-response of antiviral therapy and evaluate the potential for resistance development it is useful to determine an inhibitory quotient (IQ). (21)

The IQ is defined by the quotient C_{min}[4]/EC_{50} value, corrected for plasma protein binding. The IQ is a quotient whose numerator corresponds to concentration of the drug and whose denominator corresponds to the degree of resistance the virus has acquired. A high IQ indicates that an effective drug concentration can be achieved in a patient to inhibit the virus and minimise the development of resistance. (21,24)

Antiviral activity in vivo

If no *in vitro* cell culture has been found to be predictive of antiviral activity of the IP in humans, animal model systems can be used. Viral titres in the animal model can be

[4] C_{min}: Minimal plasma drug concentration

measured after infection and treatment with the IP to assess the antiviral activity *in vivo*. The animal pharmacokinetics (PK) can also be determined in the course of this. (21)

c) Cytotoxicity and therapeutic (selectivity) indexes

Cytotoxicity tests are important to establish that an IP has antiviral activity at concentrations that can be achieved *in vivo* without inducing toxic effects to cells and should be conducted before the initiation of phase I clinical studies. These tests use a series of increasing concentrations of the IP to determine the concentration resulting in death of 50 % of the host cells. This value is referred to as the "median cellular cytotoxicity concentration" (CC_{50} or $CCIC_{50}$). The relative effectiveness of the IP in inhibiting viral replication compared to inducing cell death (CC_{50}/EC_{50}) is defined as the "selectivity or therapeutic index" (SI)[5]. For antiviral IPs that are potential inhibitors of cellular DNA polymerases (e.g., remdesivir), that are responsible for nuclear and mitochondrial DNA synthesis, the IC_{50} values against cellular polymerases should be determined. They should show enough specificity for viral polymerase over human polymerases, especially DNA polymerase γ (responsible for mitochondrial DNA synthesis). (21)

d) *In vitro* combination activity analysis

Within an infected patient, viruses can exist as virus variants, some of which may show reduced susceptibility to one or more antiviral drugs. Therefore, for some viruses, co-administration of multiple antivirals can be more effective than monotherapy with a single product. However, there may be interactions of co-administered products and can result in antagonistic, additive, or synergistic effects concerning antiviral activity. For this reason, the *in vitro* antiviral activity of the IP in two-drug combinations with other products approved for the same indication should be evaluated. (21)

e) Resistance

Selection of resistant virus *in vitro*

The term "antiviral drug resistance" has the meaning to be caused by mutations in viral genomes that result in reduced phenotypic susceptibility to a given antiviral. The guid-

[5] Therapeutic/selectivity index: a ratio that measures the window between cytotoxicity and antiviral activity (25)

ance recommends that *in vitro* selection of resistant viruses to the IP, phenotypic and genotypic characterisation of resistant viruses, and cross-resistance analyses be examined before initiation of clinical studies in patients infected with the particular virus. (21)

Genotypic analysis

The genotypic analysis of resistant viruses selected *in vitro* can identify mutations that confer resistance to the IP. (21)

Phenotypic analysis

Phenotypic analysis determines if mutant viruses have reduced susceptibility to the IP. When mutations that may be associated with resistance are identified by genotypic analysis, the ability of each of these mutations to confer phenotypic resistance should be evaluated. (21)

Cross-resistance

Cross-resistance can be observed if antiviral drugs targeting the same protein develop mutations that lead to reduced susceptibility to one antiviral drug and can result in decreased or loss of susceptibility also to other antiviral drugs in the same drug class. The guidance recommends that the effectiveness of the IP against viruses resistant to other approved drugs in the same class and the effectiveness of the other drugs against viruses resistant to the IP should be evaluated by phenotypic analyses. (21)

3.1.1.2 Proposal for monitoring resistance development

The guidance strongly recommends that thorough resistance testing is undertaken according to the way the IP will be used in clinical practice. The knowledge of the antiviral IP's resistance patterns is later important to make the optimal treatment decision. (21)

The clinical virologic failure of IPs can be determined by measuring the viral concentration. Genotypic and phenotypic results are able to examine the emergence of resistant viruses to IPs and show a relationship between viral resistance and clinical virologic failure. (21)

It is suggested that developers submit a monitoring plan for the development of resistant viruses in clinical studies before these are initiated. The resistance monitoring plan should include the description of assays to be used to monitor viral loads. The plan should be included with the clinical development plan in the IND (investigational new drug) application. (21)

3.1.2 FDA guidance on developing drugs and biological products for treatment or prevention of COVID-19

The guidance for industry "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention" is a guidance in the context of COVID-19 for the development of drugs[6], dated May 2020. (26,27) This guidance concerns all drugs, not only antiviral drugs, for the treatment and prevention of COVID-19. However, preventative vaccines and convalescent plasma are not within the scope of this guidance. (26)

The main objective of this guidance are FDA's current recommendations regarding phase II and phase III trials to establish safety and efficacy for drugs to treat or prevent COVID-19. The focus is on the requirements of these clinical trials. (26)

a) Population

- A range of populations should be included, such as individuals in outpatient or inpatient care.
- Treatment trials for COVID-19:
  - COVID-19 should be laboratory confirmed.
  - Severity at baseline of the population should be categorised with objective criteria.
- Individuals at high risk of complications, such as elderly, persons with underlying cardiovascular disease and immunocompromised persons should be included.
- Patients with renal or hepatic impairment should be included provided the PK of the IP have been evaluated in this patient group to identify appropriate dosing regimens.
- The inclusion of pregnant and lactating women in phase III clinical trials is encouraged.

[6] „Drugs" in this guidance refers to (small molecule) drugs and biological products.

- Children:
  - Paediatric drug development should be discussed with FDA early during clinical development.
  - Under the Paediatric Research Equity Act, all MAs (Marketing Authorisation) for e.g., new active ingredients, the safety and effectiveness of the IP for the claimed indication in the paediatric populations is required and a paediatric study plan should be submitted, unless this is waived, deferred, or inapplicable. (26)

b) Trial design to examine drugs to treat or prevent COVID-19

- The recommended trial design is randomised, placebo-controlled, double-blind using a superiority design.
- All treatment arms should receive background standard of care (SOC). The SOC is expected to change as soon as new information is available.
- Duration of the trial: the trial should be last long enough to evaluate safety and effectiveness reliably, meaning the duration should be adequate to capture the majority of outcomes under COVID-19 (e.g., mortality) relevant for the patients in the trial.
- Approach if there is previous nonclinical or preliminary clinical evidence:
  - When there is convincing evidence, it may be appropriate to directly conduct larger trials.
  - If there is some but limited information on the potential for efficacy, approaches with an initial assessment of potential benefit can be made before enrolling a large number of subjects. This may be realised by a trial with an adaptive design that incorporates prospectively planned criteria either to stop the trial for lack of efficacy or the possibility of expanding from a proof-of-concept phase to a larger confirmatory trial.
- It is recommended to use an independent data monitoring committee to ensure the safety and trial integrity. The monitoring should safeguard the welfare of subjects.
- For confirmatory trials there should be prospectively planned criteria to stop the trial for lack of efficacy. The stopping criteria should aim to ensure to discontinue the trial if the drug is harmful. Part of the stopping criteria can also be the possibility of stopping the trial early due to evidence of benefit. (26)

c) Efficacy endpoints in trials to treat or prevent COVID-19

Treatment trials for COVID-19

- The drug development program should evaluate the effect of the IP compared to placebo on efficacy endpoints that are clinically important outcome measures. Examples of such efficacy endpoints are:
  - all-cause mortality
  - measures of respiratory failure: e.g., need for extracorporeal membrane oxygenation (ECMO), or non-invasive ventilation
  - measures of sustained clinical recovery
- The choice and time frame of efficacy endpoints may differ depending on the severity of COVID-19 disease in patients included in the trial. For endpoints defined by events at a specified time point the time window should be long enough to ensure possible occurrence of endpoints related COVID-19 progression.
- In a trial in severe patients, examples of appropriate end- and time points could be:
  - all-cause mortality at 28 days
  - clinical status at an appropriate time point
  - time to sustained recovery assessed during an appropriate time period

- In phase II treatment trials, a virologic endpoint (e.g., viral load) may be acceptable. However, virologic endpoints are not appropriate as primary endpoints in phase III treatment trials because there is no established predictive relationship between magnitude and timing of viral reductions and the extent of clinical benefit of the patient (e.g., survival). These endpoints can be assessed as secondary endpoints. (26)

Prevention trials for COVID-19

- Prevention trials should determine for example whether COVID-19 is milder in persons receiving prophylaxis compared with persons not receiving prophylaxis. (26)

d) Safety considerations

- A broad population of subjects should be included in clinical trials to generate a safety database.
- A standardised toxicity grading scale for adverse events (AEs) is recommended.
- The potential for drug-drug interactions that could increase the risk for toxicities should be investigated.
- Safety assessments should be performed according to severity of illness and the potential risk of the IP. (26)

e) Statistical considerations for treatment or prevention trials

Sponsors of drugs to treat or prevent COVID-19 should consider that the primary efficacy analysis should be prespecified and be conducted in an intention-to-treat (ITT)[7] population. (26)

3.1.3 FDA guidance on general considerations for pre-IND meeting requests for COVID-19 related drugs and biological products

The guidance for industry and investigators "COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products" (May 2020) has the purpose to prepare pre-IND meeting requests for COVID-19 related drugs[8]. (28) The sponsor should choose this request as mode of communication with the FDA concerning drug development of COVID-19 related drugs. This guidance should facilitate a sponsor's preparation of, and FDA's review of, a pre-IND meeting request. It remains effective only for the duration of the public health emergency related to COVID-19[9]. (28)

a) Pre-IND process

It is important that the FDA receives the key information to evaluate and manage the large number of applications from sponsors interested in conducting clinical trials for

[7] ITT: all randomised subjects. (26)
[8] "Drugs" in this guidance refers to (small molecule) drugs and biological products.
[9] The COVID-19 public health emergency was declared by the US Secretary of Health and Human Services (HHS) on 31 January 2020.

COVID-19. The pre-IND meeting can lead to a more rapid review of the later IND and the possibility of faster clinical trial initiation. Within FDA the Center for Drug Evaluation and Research (CDER) has established a multispecialty, multidisciplinary team dedicated to the review of drug development proposals due to the range in clinical manifestations of COVID-19 and the numerous drugs with many different mechanisms of actions evaluated. (28)

The pre-IND meeting request is reviewed by the FDA and generally answered as a written response only meeting. FDA's review and advice for the request will be expedited and prioritised based upon the completeness of the submission and scientific merit. Following review of the request, FDA will respond to it by working with the sponsor to ensure that all necessary information has been submitted. Focusing on the COVID-19 indication will help FDA to quickly identify, and assess the proposed trial to ensure that it is designed to address the current public health emergency and assure the safety of subjects. (28)

b) Pre-IND meeting request content

General considerations for pre-IND meeting requests

A pre-IND meeting request, instead of a pre-Emergency Use Authorization (pre-EUA) request, should be submitted for COVID-19 related drugs. Generally, there is insufficient data of the potential benefits and risks of drugs at the pre-IND stage as required for an EUA. Moreover, if a drug is appropriate for an EUA, a previous pre-IND meeting request does not preclude the future submission of an EUA request. (28)

General content

Pre-IND meeting requests should include characteristics of the IP, such as description of the active pharmaceutical ingredient (API), its manufacturing process and the dosage form of the study drug, proposed indication, summary of nonclinical and clinical data supporting the proposed use of the drug for the treatment or prevention of COVID-19. (28)

General nonclinical considerations

For the initiation of clinical studies under an IND related to treatment or prevention of

COVID-19 the sponsor should submit nonclinical data that allows FDA to evaluate the risks of the IP and to determine safe starting doses for first-in-human (FIH) trials.

The pre-IND meeting request should include furthermore:

- the planned duration of the clinical trial.
- For small-molecule (chemical) drugs: a FIH trial should be supported by a battery of nonclinical studies. In general, FDA expects data from general toxicology studies in two species (at least one nonrodent). (28)

General clinical considerations to be included in the pre-IND meeting requests

- A justification for the proposed dose, number of doses, and route of administration of drugs for treatment or prevention of COVID-19.
- A summary of the drug's safety data with previous clinical trials in other indications.
- For phase II or III trials, a randomised, placebo-controlled, double-blind clinical trial using a superiority design is recommended. A trial protocol should be submitted.
- The proposed clinical endpoints should reflect an improvement in how a trial subject feels, functions, or survives.
- The suggested size of the trial population should depend on the proposed endpoint, expected treatment effect, and the safety profile of the drug.
- A safety monitoring plan and an independent data monitoring committee is recommended. (28)

General product quality considerations in pre-IND meeting requests

The sponsor should submit sufficient information to ensure acceptable quality of the IP. (28)

Additional recommendations for antiviral drugs

Antiviral IPs can be characterised by their cell culture antiviral activity (EC_{50} value and therapeutic index) and animal model findings. However, these early antiviral activity results may not reliably predict effectiveness in humans. Therefore, the efficacy has yet to be proven in clinical trials. (28)

3.1.4 FDA's Coronavirus Treatment Acceleration Program (CTAP)

The FDA initiated the Coronavirus Treatment Acceleration Program (CTAP) on 31 March 2020 to allow the use of FDA's scientific resources and expertise for COVID-19 therapeutic development and review. CTAP focuses specifically on drugs, not vaccines or devices. CTAP regulates the development of drugs for the treatment of COVID-19. The objective of this program is to offer rapid review of possible drugs and to provide early access to them for patients, while maintaining patient safety. (16,29)

For CTAP a special e-mail inbox[10] was set up to direct the sponsor's request to the appropriate FDA division for early and low barrier discussion between the FDA and drug developers. The incoming enquiry is evaluated by a cross-functional FDA team to ensure that the enquiry is complete enough to be reviewed by FDA disease area experts. FDA experts provide regulatory advice regulatory advice (e.g., what regulatory submission is appropriate).

Once the enquiry has developed into a proposal the following key milestones can be met:

- Pre-IND meeting, where sponsors can request initial advice on their proposed development programs. For further information see *section 3.1.3* **FDA guidance on general considerations for pre-IND meeting requests for COVID-19 related drugs and biological products**.
- An IND can be applied after the pre-IND meeting. FDA's IND review ensures that appropriate safeguards for patients are in place prior to the initiation of clinical trials. For CTAP applicants compared with usual processes the FDA has significantly accelerated timelines for pre-IND meeting requests and IND review.
- "Emergency Use Authorizations (EUAs)". For an IP for which an NDA has been filed, but is not yet approved, the FDA can issue an EUA for the emergency use for COVID-19 if certain requirements are met (see *section 3.1.3* **FDA guidance on general considerations for pre-IND meeting requests for COVID-19 related drugs and biological products**).
- Filing of an NDA or BLA for the approval of drugs and biologics for use in COVID-19 patients. (16,29)

[10] COVID19-productdevelopment@fda.hhs.gov

3.2 EU/EMA: Regulatory pathways, guidance and recommendations for the development of antiviral drugs, including specific programs during the COVID-19 pandemic

The regulatory pathways of antivirals in the European Union (EU) in the pandemic are kept short, as this thesis focuses on the ones in the US.

There are no general guidelines of European Medicines Agency (EMA) for the development of antiviral medicines comparable to the FDA guidance (see *section 3.1.1* **FDA guidance on antiviral product development – conducting and submitting virology studies to the agency**). The antiviral EMA guidelines are only for antivirals against specific diseases, e.g., HIV-infection and chronic hepatitis C (CHC). (30,31) The guideline on antivirals for the treatment of CHC is given as an example below.

3.2.1 EMA guideline on the clinical evaluation of direct-acting antivirals for the treatment of chronic hepatitis

This draft guideline was released for consultation in June 2016 and is still under revision. (31) The guideline is detailed below in relation to the general aspects of antivirals against HCV and not the specific aspects of HCV for a better comparability with antivirals against COVID-19.

The scope of this guideline is to provide guidance on the drug development for the treatment of CHC, particularly for the design of clinical studies for the evaluation of DAAs against HCV. (31)

3.2.1.1 Pharmacodynamics and pharmacokinetics

3.2.1.1.1 Nonclinical virology studies

In-vitro studies of an antiviral IP against HCV should include the determination of:

- the MOA
- the $EC_{50/90}$ value in cell-based assays representing the different HCV genotypes and subtypes
- the impact of protein binding on $EC_{50/90}$
- the cytotoxicity and the therapeutic index of the drug against the same cell line

in which antiviral activity is determined

- for each viral genotype/subtype, an assessment of the in-vitro selection of resistant variants and characterisation of their phenotypic and genotypic properties.
- the activity of the new agent against viruses harbouring a range of resistance associated mutations (31)

3.2.1.1.2 Clinical virology studies

Viral drug resistance

The viral target gene of the antiviral drug should be sequenced at baseline for viruses obtained from all patients entering clinical trials. (31)

Clinical PK

To reduce the risk of selection of drug resistant variants, the initial PK studies should be performed in healthy volunteers. If it is known that the IP has a high barrier to resistance, studies in patients with hepatic impairment may be performed in patients with HCV infection. (31)

3.2.1.2 Assessment of efficacy

3.2.1.2.1 General considerations for clinical trials

For confirmatory trials randomised, active-controlled, double-blind studies with a standard-of-care regimen are recommended. In general, at least one study in which the test regimen is compared to placebo, or to an active comparator. (31)

3.2.1.2.2 Viral genotypes

The patterns of antiviral activity (EC_{50} and barrier to resistance) of many DAAs are genotype- and subtype dependent. The range of genotypes for which clinical studies are relevant for a certain drug will be determined initially on the basis of in-vitro antiviral activity data. (31)

3.2.1.2.3 Methods to evaluate efficacy, primary endpoint

The recommended primary endpoint for trials to determine the cure rate is sustained virological response[11] (SVR) 12 weeks after the planned completion of therapy (SVR12), regardless of the actual duration of treatment. (31)

3.2.1.2.4 Dose finding monotherapy studies

The dose range studied in monotherapy should be based on protein binding-adjusted EC_{50} values *in vitro* and on dose-related drug exposure data from healthy volunteers. (31)

3.2.1.2.5 Phase IIb studies and confirmatory studies

A broad range of patients should be included in confirmatory phase III studies. Therefore, an IP may be added to one or more previously approved drugs or the test regimen may consist of only two or more IPs as all effective regimens are combination regimens to date. (31)

3.2.2 EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments

The EMA guidance for the acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines was published in May 2020. (32) The guidance provides an overview of EMA's rapid review procedures to support the development and evaluation of treatments and vaccines for COVID-19. It is mainly intended as procedural guide for developers. These procedures can expedite every step of the regulatory pathway by providing efficient management of product-review activities while ensuring that medicine developers generate scientifically sound evidence on efficacy, safety and quality to support scientific and regulatory decisions. Procedures are set-up to adapt different types of review activities to the needs of the health threat. A contact point with a specific e-mail inbox (2019-ncov@ema.europa.eu) is available for developers to contact EMA early in the development process to ensure the submission of well-prepared applications and make use of the rapid procedures.

[11] SVR: HCV-RNA < lower limit of quantification (LLOQ)

The COVID-19 EMA pandemic Task Force (COVID-ETF) coordinates and enables fast regulatory action on the development of treatments and vaccines for COVID-19. COVID-ETF's activities include providing guidance on development plans of COVID-19 medicines when formal scientific advice is not yet feasible, and on product-related assessments. (32–34)

Rapid scientific advice

Rapid scientific advice is an *ad hoc* procedure that follows the scope and general principles of the regular scientific advice but with adaptations to facilitate acceleration. The final advice will be adopted by the Committee for Medicinal Products for Human Use (CHMP), but the process will also involve the additional expertise of COVID-ETF. Key features of the rapid scientific advice include flexibility regarding the requirements of the dossier, that it is free of charge, and a reduced review time of maximum 20 days (from regular 40-70 days).

The objective of this EU guidance to expedite drug development for the treatment of COVID-19 corresponds to the FDA CTAP program.

4. Drug development of remdesivir: a repurposed antiviral drug for Covid-19

4.1 Proposed mechanism of action of remdesivir

Remdesivir (RDV) was discovered amidst a screening process to identify therapeutic agents for treating RNA viruses that maintained global pandemic potential, such as those that indeed emerged later, including Ebola virus (EBOV), and the coronaviruses SARS-CoV and MERS-CoV. It was also tested against HCV and other RNA viruses, but these developments were not successful. RDV showed promise during the height of the Ebola outbreak in 2018. RDV is an inhibitor of viral RdRP. Targeting viral replication is one of the most effective anti-viral therapeutic approaches. The enzyme complex plays a key role in SARS-CoV-2 infection cycle of replication and transcription, by synthesising a complementary negative-strand RNA as a template to produce positive-strand genome for the new virions and sub-genomic mRNAs (see *section 2.3.2.3* RNA-dependent RNA polymerase (reverse transcription) inhibitors). (3,5,6,18,20,35–38)

RDV is a pro-drug of a phosphoramidate nucleoside analogue[12] (*Fig. 4*). As nucleosides are poorly cell-permeable RDV is designed to easily pass the host cell membrane by masking the charged phosphonate group[13]. Such pro-drugs are more permeable and metabolised to liberate the phosphorylated nucleoside within cells. Within human cells RDV undergoes rapid metabolic conversion steps (*Fig. 4*). First it is metabolised to the alanine metabolite (GS-704277). This metabolite is further converted into a nucleoside monophosphate (NMP; GS-441524) via esterase mediated hydrolysis, which is highly polar and remains trapped within the cell. RDV is a bio-isostere of a monophosphate and is thereby able to bypass the slow phosphorylation step to generate the nucleoside monophosphate. Finally, NMP is phosphorylated by kinases to the metabolically active nucleoside triphosphate (NTP; GS-443902) which acts as a substrate for viral RdRP and is highly selective for this polymerase compared to human polymerases (DNA and RNA polymerases). This selectivity is achieved due to the nucleoside analogue being a poor substrate for human polymerases due to the 1-CN group. The primary mechanism of inhibition is by NTP competing with endogenous adenosine triphosphate (ATP) nucleotide and being incorporated more efficiently into the growing viral RNA chain by RdRP than ATP. This results in a delayed chain-termination[14] by steric hindrance, whereby RNA synthesis is terminated after the addition of three more nucleotides as NTP inhibits the enzyme from moving forward to incorporate the next nucleotide and the replication process is suppressed. (5,6,11,18–20,37–43)

[12] Nucleoside analogue: 1-cyano-substituted adenosine

[13] Phosphoramidate pro-drugs (ProTides, inferred as pro-drugs of nucleotides). ProTides are composed of a nucleoside monophosphate capped with an aryl group and an amino acid ester (a “phosphoramidate”).(5)

[14] Delayed chain-termination is in contrast to classic nucleoside analogues that lead to immediate termination of synthesis after incorporation. (5)

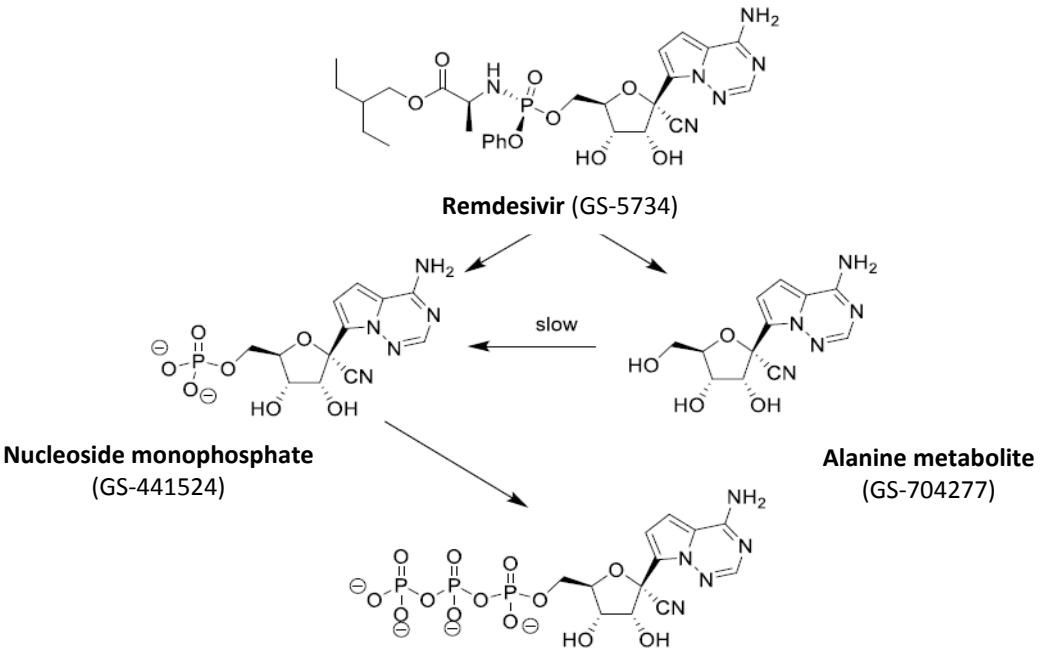

Fig. 4: Structure of remdesivir and its metabolites[15]

The efficacy of RDV is limited owing to the proofreading function of the viral exoribonuclease (ExoN). ExoN functions as a proofreading enzyme removing the incorporated RDV NTPs from the growing RNA chain. The enzyme is responsible for maintaining the stability of the virus genome, in addition it enables the excision of incorrect nucleotides. RDV is able to partly evade excision and maintain its antiviral activity in the presence of ExoN after incorporation into the RNA. The MOA of RDV might be an explanation for its increased efficiency over other nucleoside analogues by the delayed-chain termination after adding three additional nucleotides. It is assumed that these nucleotides protect incorporated RDV from ExoN excision. (6,18,20,38,39)

4.2 Nonclinical studies

4.2.1 Pharmakodynamics: antiviral activity / resistance

Antiviral activity of remdesivir

The antiviral activity of RDV both *in vitro* and *in vivo* was assessed against EBOV and clinically relevant human coronaviruses, such as SARS-CoV, MERS-CoV and human coronavi-

[15] Modified according to reference (17); "Ph" (in remdesivir structure): phenyl residue

ruses causing the common cold. However, the antiviral activity of RDV described below is limited to SARS-CoV-2. (2,8,9,17,23,35,36,40,42,44,45)

Nonclinical *in vitro* and *in vivo* studies supported the effectiveness of RDV also against SARS-CoV-2. RDV exhibited cell culture antiviral activity against SARS-CoV-2 in the following studies: An *in vitro* study investigated the impact of varying concentrations of seven test drugs, including RDV, on viral titres, cytotoxicity, and infection rates. This study was first to confirm RDV's antiviral activity against SARS-CoV-2 by inhibition of viral replication in Vero E6 cells[16], infected with a clinical virus isolate. Of these drugs RDV effectively lowered viral titres of SARS-CoV-2 at the lowest concentrations (EC_{50} of 0.77 µM) and exhibited the lowest cytotoxicity (CC_{50} > 100 µM). This resulted in a high selectivity index (SI > 129.87). Another *in vitro* in infected Vero E6 cells demonstrated that RDV reduces the viral load of SARS-CoV-2 with a ca. 30-fold higher EC_{50} (26.9 µM). However, the comparability of these results to those of the first study is limited by viral load calculations fitted to logarithmic scales[17] in the latter study, whereas in the first study viral load calculations were fitted to linear scales. In another *in vitro* study the antiviral activity of RDV against SARS-CoV-2 in both Vero E6 and human airway epithelial (HAE)[18] models was evaluated. The results showed that post-infection treatment with RDV exerts a very strong antiviral effect. (2,5,9–11,19,25,35,39,41,44,45)

The prophylactic and therapeutic efficacy of RDV was evaluated in infected rhesus macaque monkeys (non-human primates, NHP). These models more accurately recapitulate the lung disease observed in humans with SARS-CoV-2 infection (or MERS-CoV, SARS-CoV) compared to rodents primarily used for animal models. First, high levels of serum esterases rapidly degrade the pro-drug RDV in rodents. Second, the active NTP of RDV has a significantly shorter $T_{½}$[19] in the mouse lung compared to human lung cells and lungs of NHP. Therefore, there was no suitable rodent model to study the efficacy of RDV *in vivo*.

[16] Vero cells: a cell line originating from African green monkey kidney epithelial cells. This cell line supports viral entry of SARS-CoV-2 by a high expression of ACE2 receptor (10,11,44)
[17] log_{10} viral RNA copies/ml (44)
[18] The EC_{50} of RDV against a clinical isolate of SARS-CoV-2 in primary HAE cells was 9.9 nM 48 hours post-treatment. (9)
[19] $T_{½}$: elimination or plasma half-life; length of time required for the concentration of a drug to decrease to half of its starting dose in the body.

Dosing and PK analyses in NHPs can serve as a bridge to human dosing regimens. However, due to the more rapid infection course in the monkeys, the optimal treatment time points that are calculated based on expected viral load peaks cannot be directly translated to humans. (2,5,9–11,19,25,35,39,41,44,45)

The *in vivo* study with rhesus monkeys evaluated the effect of RDV treatment on COVID-19 outcome. Animals were infected with SARS-CoV-2 and then given intravenous placebo or RDV. The monkeys were treated when maximum viral titres are expected at 12 h post-infection with a loading dose of 10 mg/kg (day 1) followed by 5 mg/kg daily (day 2-6). The dosing is a PK bridge from rhesus monkeys to humans as this dose is equivalent to that recommended for humans. In contrast to animals given placebo (n=6), animals treated with RDV (n=6) did not exhibit signs of respiratory disease, had lower lung virus titres and less lung tissue damage on day 7 after inoculation. In summary, treatment with RDV initiated early during infection exerts a clear clinical benefit in SARS-CoV-2-infected monkeys compared to the placebo group. This study supports the early initiation of RDV treatment for COVID-19 patients to prevent disease progression. This finding suggests proof-of-concept antiviral activity against SARS-CoV-2, along with the safety profile of RDV in the clinical trial assessment against EBOV supported the evaluation of RDV as a potential therapeutic drug for repurposing against SARS-CoV-2. (2,5,9–11,19,25,35,39,41,44,45)

SARS-CoV-2 resistance to remdesivir

Nucleoside analogues, such as RDV, are generally expected to have a higher barrier to antiviral resistance than other antivirals due to their well-conserved target RdRP. This is countered by the effect of the ExoN enzyme that removes incorrectly incorporated nucleotides (see *section 4.1*). However, the relatively modest effect of ExoN on susceptibility to RDV is attributed to the highly selective incorporation of RDV NTP into RNA compared to natural ATP and to the mechanism of delayed chain termination by RDV (see *section 4.1*).

Another factor are amino acid substitutions in the RdRP polymerase domain that will probably result in decreased susceptibility. Substitutions at homologous SARS-CoV amino acid residues in the neighbourhood of RdRP conferred a 6-fold reduction in susceptibility

to RDV in cell culture (EC_{50}: 0.01-0.06 µmol/l). However, the mutant viruses showed reduced viral fitness, with wild-type virus outcompeting the mutants in the absence of RDV. Similar results are also expected concerning SARS-CoV-2 but no cell culture development of SARS-CoV-2 resistance to RDV has yet been published and no clinical data are available on this. In summary, RDV has a high genetic barrier to resistance development, and known resistant virus variants suffer from a loss of viral fitness. IP's that are able to block the target ExoN and prevent proofreading would be of interest for combination therapy as they significantly increase virus susceptibility to RDV *in vitro*. (39,43,44)

4.2.2 Nonclinical toxicology

General nonclinical pharmacology/toxicology considerations

Nonclinical safety studies were conducted in rats and cynomolgus monkeys for up to 4 weeks. The kidney was identified as the target organ of toxicity in animals. (9)

Reproductive and developmental toxicology

A reproductive and development toxicity program has not identified any adverse effects in pregnant rats and rabbits at nontoxic doses of RDV on embryo-foetal development of their off-spring[20]. (9,43)

Carcinogenesis and mutagenesis

Given the short-term administration of RDV for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential were not conducted. RDV is not considered a potential mutagen or clastogen based on a battery of *in vitro* and *in vivo* assays[21] performed to assess its genotoxic potential. (9,43)

4.2.3 Animal toxicology and pharmacokinetics of RDV

RDV was administered IV to male rhesus monkeys at dose levels between 5 and 20 mg/kg/day for 7 days. At all dose levels this resulted in kidney-related effects, such as in increased mean creatinine and renal tubular atrophy. These effects were observed at

[20] On embryo-foetal (rats and rabbits) or pre/post-natal (rats) development (9)
[21] In vitro assays: bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes; in vivo assays: rat micronucleus assays (43)

exposures of the NMP metabolite of RDV that are lower than the exposure in humans at the recommended human dose. (43)

NHPs are considered the most suitable animal model for evaluating the PK properties of RDV. Pharmacokinetics studies in NHP monkeys orally administered RDV indicated a low bioavailability due to the near complete first-pass effect of phosphoramidates. PK parameters and metabolism of RDV was studied in healthy rhesus monkeys given 10 mg/kg RDV IV. The plasma half-life of the prod-drug RDV was short (T½: 0.39 h). RDV was rapidly distributed into peripheral blood mononuclear cells (PBMC) and converted to the main metabolite NTP with sustained intracellular levels (T½: 14 h). The plasma concentration of NTP was higher than the EC_{50} over 24 h. Additional studies have shown that C_{max}[22] of NTP in the plasma of rhesus monkeys after 10 mg/kg RDV is 30-40 µmol/l. Distribution was studied in cynomolgus monkeys by IV injection of RDV. RDV and its metabolites distributed into favourable organs for viral replication, such as testes, epididymis, eyes, and brain 4 hours after a 10-mg/kg dose.

In summary, the PK data indicated that the RDV dose used in clinical studies could provide effective intracellular NTP levels and thus exerts antiviral effects. (5,19,39,45)

4.3 Clinical trials

4.3.1 Phase I pharmacokinetic trials with remdesivir in humans

Phase I trial during Ebola virus disease epidemic

In a blinded, randomised, placebo-controlled phase I trial of RDV its safety, tolerability, and PK in healthy adult volunteers was evaluated during the Ebola virus disease (EVD) epidemic. The single-dose of 3-225 mg RDV given IV was well tolerated. The multiple-dose administration of 150 mg RDV IV once daily for 7 or 14 days was also well tolerated. Most frequent AEs in this trial were reversible low grade (1-2) elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (both markers for impaired liver function) for several volunteers. (19)

[22] C_{max}: Maximal plasma drug concentration (39)

Further phase I PK trials

In general, the number of phase I trials of RDV performed during the COVID-19 pandemic is limited due to the available clinical experience during the EVD epidemic.

Elimination

RDV has a short plasma half-life (T½: ca. 1 h), followed by the NMP metabolite with a longer plasma half-life (T½: ca. 27 h) and the active NTP with a prolonged intracellular T½ (PBMC T½: ca. 40 h). RDV and NMP exhibit linear PK following single doses (3-225 mg)[23]. After once daily dosing RDV does not accumulate, whereas NMP reaches steady state around day 4 and accumulates by ca. 2-fold after multiple dosing. Therefore, a maintenance dose of 100 mg is recommended after a loading dose of 200 mg to maintain an effective blood concentration. (9,17,19,39,45)

PK parameters

The plasma PK parameters $C_{max,}$ T½ and AUC[24] of RDV and the NMP metabolite were derived from single- and multiple-dose studies in human healthy volunteers (see *Table 1*). These studies showed that C_{max} values achieved are many folds above concentrations required *in vitro* to inhibit SARS-CoV-2 replication by 50% (EC_{50}: 0.137–0.77 µmol/l; see above in this section). The RDV dosing regimen evaluated in clinical trials and equivalent to the approved recommended dose (200 mg IV[25] on day 1, then 100 mg IV on days 2 through 5 or 10) was substantiated mainly by bridging PK data from rhesus monkeys to humans. (39)

Table 1: Multiple dose PK parameters of RDV[26] and the NMP metabolite following IV administration of RDV 100 mg to healthy adults

Parameter Mean (CV%)		**RDV**	**NMP metabolite**
C_{max}	(ng/ml)	2229 (19.2)	145 (19.3)
AUC_{tau}	(ng•h per ml)	1585 (16.6)	2229 (18.4)
C_{trough}	(ng per ml)	ND	69.2 (18.2)

Table modified according to (9); CV: Coefficient of Variation; ND: Not detectable (at 24 hours post-dose)

[23] Trial GS-US-399-1812 (19)
[24] AUC: area under the concentration time curve (39)
[25] IV: intravenous
[26] RDV administered as a 30-minute IV infusion

Absorption

As in NHP RDV is expected to have poor oral bioavailability in humans. Moreover, the oral administration to infected patients might not be ideal because severe gastrointestinal symptoms could limit the effective absorbed dose. Therefore, IV injection is the appropriate administration route of RDV. (19,39,40)

Distribution

Plasma protein binding (PPB) for RDV is moderate (88-93.6%). By contrast, the NTP metabolite exhibits low PPB (ca. 2%). Distribution studies in humans have not yet been reported. (9,39)

Metabolism

In vitro, RDV is a substrate of several cytochrome P450 (CYP) enzymes (e.g., CYP3A) and is an inhibitor of several enzymes (e.g., CYP3A4). However, the clinical relevance of these *in vitro* assessments has not been established. Therefore, it is expected that the effect of hepatic impairment on RDV plasma levels is low. It is possible that RDV metabolites that have a longer T½ than RDV also are CYP substrates, however their metabolism has not been characterised. (9,39)

Excretion

The main route of elimination for RDV is metabolism, whereas for the NMP metabolite it is glomerular filtration and active tubular secretion (49%). Dose recovery of RDV in faeces is ca. 18%. A small amount of RDV is excreted renally (< 10%). In patients with renal impairment plasma exposure of NMP may be increased. RDV formulations contain sulfobutylether-β-cyclodextrin sodium (SBECD) as a solubility enhancer. Formulations containing SBECD have been warned of in the past for patients with renal impairment because it is renally cleared and accumulates in patients with decreased renal function. Therefore, the FDA-approved prescribing information (PI) of Veklury[27] does not recommend the product

[27] Veklury™: contains RDV and was approved in the USA on 22 Oct. 2020. The Marketing Authorisation Holder is Gilead Sciences Inc. (9)

in patients with severe renal impairment (eGFR[28] < 30 ml/min). Currently there are no recommendations for dose adjustments in patients with mild to moderate renal impairment. At FDA approval, there were no dedicated studies conducted in patients with renal or hepatic impairment. Currently, there is insufficient evidence to conclude that hepatic or renal impairment will not affect PK of RDV. (9,39,43,46)

Adverse events from phase I PK trials

Four phase I clinical PK trials were conducted to evaluate the safety, tolerability, and PK of RDV after COVID-19 outbreak[29] in a total of 138 patients, of whom 131 received RDV and 7 received placebo. Overall, the drug is generally well tolerated. AEs (pooled data) occurred in only a few cases, most frequently phlebitis (8 subjects), constipation (7), headache (6), ecchymosis (5), nausea (5), and pain in extremities (5) occurred. A few grades 1 and 2 laboratory abnormalities included transient elevations of ALT/AST levels (12), mild reversible prolongation of the prothrombin time without changes in international normalised ratio (INR) (7), and mild hyperglycaemia (4). There were no signs of nephrotoxicity in healthy subjects and no patterns of clinically relevant changes in vital signs or electrocardiograms. (44)

4.3.2 Phase II and III trials with remdesivir

4.3.2.1 Phase II-III trial for Ebola virus disease

The safety and PK of RDV have been evaluated in both single- and multiple-dose phase I and phase II clinical trials for EVD during the last decade. (17,19)

The largest clinical trial for EVD was a phase II-III trial in 2018/2019 in the Democratic Republic of the Congo (see *section 4.1*). The evaluation under the FDA's Animal Rule was requested, permitting the reliance on efficacy findings from animal studies for drugs in which it is not feasible or ethical to conduct trials in humans. Regarding this, RDV was included in a randomised, controlled trial of four treatments in an open-label parallel 1:1:1:1 design in 681 EBOV positive patients. Patients received either RDV, a single monoclonal antibody (Mab), a combination of 3 Mabs, or the triple Mab complex ZMapp (con-

[28] eGFR: estimated glomerular filtration rate (43)
[29] GS-US-399-1812, -1954, -4231, and -5505

trol group). The primary efficacy endpoint was the mortality rate after 28 days, the secondary endpoint was the time from enrolment to the time when EBOV test results became negative. An interim analysis found RDV with respect to the mortality rate inferior to the other two trial drugs[30]. Subsequently, the RDV arm was terminated. Although the efficacy of RDV treatment was inferior compared to the antibody therapies, the RDV arm did provide an insight into the safety profile. One serious AE of hypotension that led to a fatal cardiac arrest was reported. This AE was judged that the death could not be clearly be distinguished from underlying fulminant EVD. Other AEs were elevated creatinine (marker for impaired kidney function) and AST levels in the RDV arm compared to the two intervention arms. The clinical development of RDV for EVD was stopped. As this study did not include a placebo control arm no conclusions can be drawn on the efficacy against EBOV. (5,10,19,44)

4.3.2.2 Phase III trials for COVID-19

Only the phase III trials are described within the scope of this thesis. A phase I trial of RDV was not conducted because phase I trials had already been performed during the EVD epidemic. (19)

Trials without control group

SIMPLE I trial: RDV 5-day vs. 10-day regimen[31]

A multinational[32], multicentre, randomised, open-label phase III trial (sponsor: Gilead Sciences) evaluated the optimal treatment duration with RDV. The trial was designed to assess for superiority of the 10-day RDV regimen[33] (n=197) over the 5-day regimen (n=200) by comparing the clinical improvement on day 14 (primary endpoint)[34] in hospitalised patients with severe COVID-19. Both groups received additionally SOC. Secondary endpoints included rates of AEs, additional measures of clinical response and death. Superiority for clinical improvement was not demonstrated and patients receiving a 5-day

[30] The mortality rate at 28 days in the RDV arm was 53%, which was significantly higher than in the other two intervention arms (34% and 35%) and the control group (49%). (5)
[31] US ClinicalTrials.gov: NCT04292899; GS-US-540-5773
[32] Conducted in 15 countries. (37)
[33] 200 mg RDV on day 1, followed by 100 mg on days 2-5 (5-day regimen) or days 2-10 (10-day regimen) in single daily IV infusions.
[34] Odds Ratio (OR) for clinical improvement defined as an improvement of at least two points on a 7-point ordinal scale on day 14 (1 = death; 7 = not hospitalised) (37)

regimen of RDV had a similar clinical status at day 14 as those receiving a 10-day course[35]. Clinical recovery (secondary endpoint) by day 14 was 64.5% vs. 58.3% in the 5-days vs. the 10-days group, respectively. A subgroup analysis of pooled data from both arms of this study suggested a greater benefit, if RDV was initiated early within 10 days of symptoms. The mortality rate (secondary endpoint) was comparable in the RDV 5-day group (12%) and the RDV 10-day group (14%). Overall, results in this trial were suggestive of similar treatment effects with 5-day and 10-day regimens in this patient population. It is possible that the open-label trial design influenced the differences in outcomes demonstrated in this trial, with numerical difference favouring the 5-day RDV group over the 10-day RDV group. Hence, discharge decisions may have been influenced by the patients' treatment assignment, which could potentially impact the overall results. An additional limitation of this trial is absence of a control group (SOC alone). Hence, it is not possible to draw conclusions from this trial on the overall efficacy of both regimens. The most common AEs were nausea (9%), worsening of respiratory failure (8%) and elevated AST levels (7%). (9,11,37,40,42,44,47)

SOLIDARITY trial[36]

The WHO-led, multicentre, open-label, randomised SOLIDARITY trial compared different investigational interventions plus SOC to SOC alone in hospitalised patients with Covid-19. One of the trial drugs was RDV. Interim results report that 301 (11.0%) of 2743 patients who received RDV and 303 (11.2%) of 2708 patients analysed who received SOC alone died by day 28[37]. The primary endpoint was in-hospital mortality at day 28. No statistically significant difference in mortality[38] was found between the RDV and SOC groups. However, subgroup analysis of oxygen supply of patients at baseline showed a trend towards reduced mortality with RDV among patients requiring low-flow or high-flow oxygen at baseline, but not among those requiring mechanical ventilation at baseline. From this finding early administration of RDV after infection seems to be more effective. However, also this trial did not include a control group and it is not possible to draw conclusions on the efficacy of RDV. (48–50)

[35] OR: 0.75 (95% confidence interval [CI]: 0.51-1.12 (37)
[36] US ClinicalTrials.gov: NCT04647669 (48)
[37] Kaplan-Meier rate ratio (RR) 0.95 (95% CI 0.81-1.11; p=0.50) (48)
[38] 12.2% in the RDV group vs. 13.8% in the placebo group (RR: 0.85, 95% CI: 0.66-1.09) (48)

Randomised controlled clinical trials (RCT)

RDV was evaluated in three RCT. (11)

First phase III, randomised, placebo-controlled trial in China[39]

This first phase III, randomised, double-blind, placebo-controlled, trial with RDV vs. placebo adults (mean age 65 years) with severe COVID-19[40] started in Wuhan/China in February 2020. Supplementary medicine[41] was allowed in both groups. The primary endpoint was median time to clinical improvement[42] within time period until day 28. No significant difference was found in the primary endpoint between the treatment groups[43]. Moreover, no significant difference in the of 28-day mortality and time to viral clearance (both secondary endpoints) were observed between the treatment groups. The trial was stopped pre-term in March 2020 due to insufficient recruitment of patients when the outbreak became controlled (n=237; RDV: n=158; placebo: n=79), although the calculated target enrolment size was 453 patients. Therefore, the trial was statistically underpowered and results remained inconclusive. Also, with concomitant medication, such as corticosteroids and other antivirals, results of the RDV effect cannot be conclusively assessed. It is noteworthy though that of all clinical trials on RDV only this trial reports on its impact on viral load. The number of AEs reported in the RDV group were nearly identical to the ones in the placebo group (102/158 (66%) vs. 50/79 (64%) patients). In both groups most frequently constipation, hypoalbuminemia, hypokalaemia, and anaemia occurred. Serious AEs were reported in 18% of patients treated with RDV and 26% assigned to placebo but discontinuation was more frequent with RDV (12% vs. 5%). No deaths were judged as being possibly related or related to treatment. (11,37,40,44,46,48)

[39] US ClinicalTrials.gov: NCT04257656 (11)

[40] Inclusion criteria: laboratory-confirmed SARS-CoV-2 infection, an interval from symptom onset to enrolment of ≤ 12 days, oxygen saturation ≤ 94% on room air or arterial oxygen partial pressure/fractional inspired oxygen ratio ≤ 300mmHg, and radiologically-confirmed pneumonia (46)

[41] Concomitant medication included corticosteroids, interferon alfa-2b, lopinavir/ritonavir and antibiotics.

[42] Clinical improvement: a two-point improvement on a 6-point ordinal scale of clinical status [1□discharged from hospital; 6□death] or live discharge from the hospital) (46)

[43] 21.0 days for RDV vs. 23.0 days for placebo; hazard ratio (HR): 1.23, 95% CI: 0.87-1.75 (37,44)

Adaptive COVID-19 Treatment Trial 1 (ACTT-1)[44]

This pivotal phase III trial was initiated by the US institute NIAID[45]. The design of this trial was adaptive[46], multinational[47], multicentre, randomised, double-blind, placebo-controlled to evaluate RDV treatment in hospitalised adults (mean age 59 years) with mild, moderate or severe COVID-19. It included 1062 patients were randomised in a 1:1 ratio to receive RDV (541) or placebo (521). For both groups use of concomitant therapy[48] was possible. The treatment regimen consisted of an initial dose of 200 mg of RDV on day 1 followed by a maintenance regimen of 100 mg on days 2-10 in single daily IV infusions. The primary endpoint was time to recovery through day 29[49]. A key secondary efficacy analysis was the classification of recovery at day 15 using a proportional odds of improvement scale. All-cause mortality at day 14 and 29 were also pre-specified secondary endpoints. An interim analysis after completion of enrolment was published by the Data and Safety Monitoring Board on 29 April 2020. In this interim evaluation, treatment with RDV was associated with a significant reduction in median time to recovery from median 15 to 11 days (31% faster time to recovery for RDV vs. placebo)[50]. Based on these preliminary results, FDA issued an EUA for RDV 2 days after the press release and RDV was approved by conditional MA by the EMA (see *section 5.1.2* **Decreasing application review time***).* In the final analysis the median time to recovery was even faster with 10 days in the RDV group versus 15 days in the placebo group (RRR: 1.29; 95% CI: 1.12-1.49; $p < 0.001$). Subgroup analyses showed that patients with severe disease and require oxygen above their baseline at enrolment benefit most from the treatment (median time to recovery: 11 days (RDV) vs. 18 days (placebo); RRR: 1.31 [95% CI: 1.12-1.52]). The key secondary endpoint of odds of improvement at day 15 also significantly favoured RDV over placebo. There was a numeric difference in the 29-day mortality rate favouring RDV, but this difference was not statistically significant (11.4% of patients in the RDV group vs. 15.2% in

[44] US ClinicalTrials.gov: NCT04280705 (11)
[45] NIAID: National Institute of Allergy and Infectious Diseases; part of the National Institutes of Health (NIH) (11)
[46] Adaptive design: a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. (51)
[47] Trial conducted at 68 sites (80% in the US, 15% in Europe and 5% in Asia). 53% were white, 21% black, 13% Asian, 24% were Hispanic or Latino. (9,37,46)
[48] About a quarter were receiving invasive mechanical ventilation, 19% required high-flow nasal cannula or non-invasive mechanical ventilation, and 40% required oxygen supplementation.
[49] The day of recovery was defined as the first day one of the categories were met in an ordinal scale: Hospitalised, for infection control purposes only, not requiring supplemental oxygen or medical treatment; or Not hospitalised, with or without limitation on activities and/or requiring oxygen at home. (9,37,42,46,48)
[50] Recovery rate ratio [RRR] 1.32 [95% CI: 1.12-1.55; $p < 0.001$] (9,37,42,46,48)

the placebo group). However, among the subset of patients with better disease progression[51] RDV had a significant mortality benefit[52]. The incidences of most AEs were not found to be significantly different among the treatment and placebo groups. Severe (grade 3) to potentially life-threatening (grade 4) AEs in general and some AEs, such as anaemia or increased ALT/AST levels occurred slightly more often in the placebo group than in the RDV group. Other AEs occurred slightly more often in the RDV group (increased creatinine levels, pyrexia, and hyperglycaemia). (9,11,37,40,42,44,46–48)

SIMPLE II trial: RDV 5-day vs. 10-day regimen[53]

This phase III, multinational, randomised, open-label, controlled trial (sponsor: Gilead Sciences) evaluated the safety and efficacy of 5 days *versus* 10 days of RDV compared to SOC in hospitalised patients with moderate COVID-19[54]. Patients (n=596) were randomised in a 1:1:1 ratio to receive a 10-day course of RDV[55] (n=197), a 5-day course of RDV (n=199), or SOC (n=200) as control group. The primary endpoint was the odds of improvement of clinical status on day 11 on an ordinal scale (same scale as for above mentioned SIMPLE I trial). This trial demonstrated a statistically significant difference in the odds of improvement at day 11 favouring the 5-day treatment group over SOC[56] (odds ratio 1.65 [95% CI: 1.09-2.48, p=0.02]). However, the clinical significance of this result remains unclear because for the 10-day treatment group the odds of improvement in clinical status *versus* the control group were not statistically significant. A limitation of this trial is the open-label design as for the SIMPLE I trial which may have influenced the differences in outcomes demonstrated in the RDV 5-day and RDV 10-day groups. The most common adverse reaction in the RDV groups was nausea (7% in the 5-day, 4% in the 10-day group). (9,11,37,42)

[51] Requiring oxygen supplementation but not high-flow oxygen or ventilatory support (48)
[52] 4.0% in the RDV group vs. 12.7% in the placebo group (HR: 0.30; 95% CI 0.14-0.64) (46)
[53] US ClinicalTrials.gov: NCT04292730; GS-US-540-5774
[54] Patients hospitalized but not requiring supplemental oxygen. (9)
[55] 200 mg RDV on day 1, followed by 100 mg on days 2-5 (5-day regimen) or days 2-10 (10-day regimen) in single daily IV infusions.
[56] Odds ratio: 1.65 (95% CI: 1.09-2.48, p=0.02) (37)

4.3.3 Overall adverse events from clinical trials with RDV

In summary, RDV shows an acceptable safety profile from clinical trials. There is no evidence for grade 3 to 4 AEs resulting from once-daily doses of RDV (75 mg up to 225 mg IV) for treatment durations of up to 14 days in phase I trials with healthy volunteers. The major safety issues identified were hepatotoxicity and hypersensitivity reactions. Hepatotoxicity, manifested as transient mild (grade 1) to moderate (grade 2) elevations in ALT in transaminase (ALT/AST) levels, appears to be related to both increasing dose and duration of administration. Hepatic safety data from trials in COVID-19 are difficult to evaluate as hepatic injury is a common feature of COVID-19. Given the findings in the phase I trials, a warning for hepatotoxicity is included in the PI. This warning is a recommendation to perform hepatic laboratory testing before and during RDV treatment as clinically appropriate. Furthermore, it is recommended to discontinue RDV if ALT levels increase to > 10 times ULN[57] and to discontinue RDV when signs or symptoms of liver inflammation occur. Hypersensitivity reactions[58], including infusion-related and anaphylactic reactions, were reported during and following administration of RDV in clinical trials and under the EUA. Signs and symptoms included hypotension, dyspnoea, angioedema, rash and nausea. Regarding renal toxicity a renal safety signal was identified in nonclinical studies. However, no clear renal safety signal was apparent in either healthy volunteers or COVID-19 patients. The PI recommends the determination of the eGFR before initiating RDV and during treatment as clinically appropriate. Due to the addition of SBECD in the solution RDV is not recommended if eGFR is < 30 ml/min (see *section 4.3.1* **Phase I pharmacokinetic trials with remdesivir in humans**). Concerning prothrombin time (PT) elevation in the ACTT-1 trial, a disproportionate percentage of PT elevations occurred in the RDV group *versus* the placebo group. However, no increased risk of clinically significant haemorrhagic AEs was detected. As a precaution the PI includes a recommendation to determine PT in all patients prior to starting RDV and to monitor PT during treatment. The nature and frequency of other significant AEs (deaths, serious AEs, and discontinuations due to AEs) reported in the phase III trials largely reflect the symptoms of the underlying disease. There are not sufficient data on the safety of RDV in patients younger than 18 years

[57] ULN: upper limit of normal

[58] Signs and symptoms included hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. (9)

of age and pregnant women. Long-term toxicities are known from other nucleoside analogues used for sustained antiviral treatments of chronic infections with HIV or HBV but should not be of relevance for the relatively short-term treatments with RDV. Possible AEs that did not appear during the pre-approval trials can be identified by post-marketing surveillance and risk assessment programs. (9,44,50)

4.3.4 Overview of described phase III trials with remdesivir for COVID-19

The phase III trials with RDV for COVID 19 described above are summarised in *Table 2*.

Table 2: Phase III trials with RDV for the treatment of COVID-19

Trial name: short description (number[2])	Trial design	Severity of COVID-19	Treatment arms (n[3]) (randomisation ratio)	Primary efficacy endpoint	Main results
Trials without control group					
SIMPLE I: RDV[1] 5-day vs. RDV 10-day regimen (NCT04292899)	mc, ra, open[4]	Severe	10-day RDV (197) vs. 5-day RDV[5] (200) (1:1)	Clinical improvement on day 14	Non-superiority for clinical improvement at day 14 of the 5-day RDV regimen vs. the 10-day RDV regimen.
SOLIDARITY (WHO) (NCT04647669)	mc, ra, open	Differing grades of severity	RDV plus SOC[6] (2743) vs. different trial drugs plus SOC vs. SOC alone (2708) (RDV/SOC alone: 1:1)	In-hospital mortality at day 28	No significant difference in mortality found between the RDV and the SOC group.
Randomised controlled clinical trials (RCT)					
First phase III RCT in China (NCT04257656)	ra, db, plac[7]	Severe	RDV (158) Plac (79) (2:1)	Median time to clinical improvement within period until day 28	No significant difference in time to clinical improvement found between the RDV and the placebo group.
ACTT-1 (NCT04280705)	adaptive, mc, ra, db, plac	Mild, moderate or severe	RDV[8] (541) Plac (521) (1:1)	Median time to recovery within period until day 29	Median time to recovery was significantly faster in the RDV group (10 days) vs. the placebo group the (15 days)
SIMPLE II: RDV[2] 5-day vs. RDV 10-day regimen (NCT04292899)	mc, ra, open, controlled	Moderate	10-day RDV (197) vs. 5-day RDV[5] (199) vs. Control: SOC (200) (1:1:1)	Odds of improvement of clinical status on day 11	Significant difference in odds of improvement at day 11 favouring the 5-day RDV over the SOC group. For the 10-day RDV vs the SOC group the difference in odds of improvement was not significantly different.

[1]RDV: remdesivir;[2]: Trial number according to US ClinicalTrials.gov; [3]n: number of patients treated; [4]: mc: multicentre; ra: randomised; open: open-label; [5]: 200 mg RDV on day 1, followed by 100 mg on days 2-5 (5-day regimen) or days 2-10 (10-day regimen) in single daily IV infusions. 6: SOC: standard of care; [7]: db: double-blind; plac: placebo-controlled; [8]: 200 mg RDV on day 1 followed by 100 mg on days 2-10;

4.3.5 Trials as basis of the FDA approval of Veklury™ (RDV)

RDV is active *in vitro* against various CoVs, including SARS-CoV-2, and its MOA is well elucidated. Animal studies that included NHP models of SARS-CoV-2 support its efficacy, especially when administered early in the course of the disease. (44)

The FDA approved Veklury (RDV) as the first drug for the treatment of COVID-19 on 22 October 2020. The approval was based on the three key phase III clinical trials supporting an indication for RDV for the treatment of COVID-19 in hospitalised patients of varying disease severity:

- The pivotal RCT designated ACTT-1 had a rigorous trial design, large sample size, and broad patient population provided the most objective assessment of efficacy. It demonstrated a highly statistically significant difference in time to recovery (primary endpoint) as well as the key secondary endpoint of odds of improvement at day 15. There was a numeric difference in mortality favouring RDV over placebo; however, this difference was not statistically significant.

  The FDA compared the outcome of this trial with the one of the SOLIDARITY trial. Common to both trials is that they did not find a statistically significant difference in mortality between the RDV and the control group (SOC or placebo). However, the two clinical trials had different trial designs and primary endpoints. ACTT-1 was not powered to evaluate mortality and the trial design was better suited to rigorously assess time to recovery and odds of clinical improvement endpoints compared to a trial with an open-label design, such as the SOLIDARITY trial. Based on the findings of the ACTT-1 trial, benefit to patients for RDV was demonstrated for these endpoints and additionally, this may help to reduce the number of inpatient days, with positive effects on intensive care capacity issues and costs. The SOLIDARITY results do not contradict these findings of benefit to patients.
- The supportive SIMPLE I trial assessed for superiority of the 10-day RDV regimen over the 5-day RDV regimen. Superiority was not demonstrated and results were suggestive of a similar treatment effect with 5-day and 10-day regimens. However, the open-label design and absence of a SOC control arm limits the interpretability of the data.

- The supportive RCT SIMPLE II trial included a SOC control arm and demonstrated a statistically significant difference in the odds of improvement at day 11 favouring the 5-day (but not the 10-day) treatment group over SOC. Despite the inherent limitations of its open-label design, this trial provided supportive evidence for the efficacy of RDV in patients hospitalised with COVID-19 of moderate severity.

In these three trials RDV demonstrated efficacy in treating hospitalised patients with COVID-19. An uncertainty remained surrounding:

1) the optimal duration of therapy for patients hospitalised with COVID-19. The FDA recommended that patients who do not need mechanical ventilation ECMO should receive RDV for 5 days. If a patient does not demonstrate clinical improvement treatment can be extended to up to 10 days. The flexible recommended duration of treatment reflects the balance of efficacy and safety considerations. For hospitalised patients who require mechanical ventilation or ECMO the recommended treatment duration is 10 days.

2) the impact of RDV on virologic parameters as clinical virology data was not submitted.

Furthermore, doubt remained surrounding the optimal dosing of RDV in paediatric patients, pregnant patients, and in patients with renal or hepatic impairment. No dedicated hepatic or renal impairment trial, or any clinical drug-drug interaction (DDI) trials had been conducted. A trial in pregnant patients was planned. These uncertainties resulted partly from the important public health priority of expediting the review of a safe and effective therapeutic in the setting of an unmet medical need and were addressed as post-marketing requirements (PMRs) and post-marketing commitments (PMC). PMRs include the conduct of clinical trials in paediatric patients with COVID-19 and in patients with renal or hepatic impairment, a dedicated QT trial, and a DDI trial to evaluate the PK of RDV when co-administered with rifampin. A PMC was issued for a clinical trial to collect PK and safety data in pregnant patients.

The FDA assessed the overall benefit-risk profile of RDV as favourable and approved it for an indication for adults and paediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalisation.[59] (9,43,44,47,49,50)

[59] Veklury™ is available in two dosage forms: 1) Veklury for injection™: 100 mg lyophilized powder in vial. The powder needs to be reconstituted with Sterile Water for Injection prior to diluting in a 100 ml or 250 ml

4.4 Conclusions and outlook for the treatment of COVID-19 with remdesivir

RDV is the first DAA to treat infections caused by a respiratory virus. It is effective mainly for patients with severe COVID-19, requiring supplemental oxygen and shortens the time to subjective improvement. However, RDV does not have a mortality benefit and does not reduce the risk to require mechanical ventilation. Moreover, the use of RDV in an outpatient population is prevented by its poor oral bioavailability and the lack of an oral formulation. (44) Moreover, also drug pricing has significant implications for the possibility of applying RDV with a broader scope. In this respect, the costs of RDV treatment per patient is very high (ca. 2,350 $). These costs are not feasible for developing countries. The WHO currently recommends against the use of RDV for any severity. (9,44,49,52)

The therapeutic efficacy of RDV might be improved by the combination with other antivirals or immunomodulatory agents, such as glucocorticoids. However, combination therapy should be used with caution, as drug interactions may occur. For example, the concomitant use of RDV with chloroquine or hydroxychloroquine reduces RDV's antiviral activity. An approach that may improve clinical outcomes could be combination therapy with DAAs that target several processes within the viral life cycle. This strategy is highly effective in the therapy of chronic infections with HIV and HCV. In November 2020 the FDA authorised an EUA of baricitinib in combination with RDV for the treatment of certain hospitalised patients[60] with suspected or laboratory-confirmed COVID-19. Baricitinib is a janus kinase inhibitor, which blocks specific enzymes, interfering with the pathway that leads to inflammation. This was FDA's first authorisation of a drug that acts on the inflammation pathway of COVID-19. Baricitinib was repurposed from the FDA-approved indication for rheumatoid arthritis. (9,44,49,52)

0.9% sodium chloride infusion bag. 2) Veklury injection™: 100 mg/20 ml solution in vial. The solution must be diluted in a 250 m 0.9% sodium chloride infusion bag. (43)

[60] Hospitalized adults and paediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO. (52)

4.5 Conformities and deviations of remdesivir's drug development from FDA regulatory pathways and guidance

4.5.1 FDA guidance on antiviral product development

The FDA guidance on antiviral drug development is a general development guideline for antivirals against human viruses. (21) In the following, the conformities or deviations of the drug development of RDV with the individual points of the guideline are described.

4.5.1.1 Nonclinical virology studies

a) MOA studies

The MOA of RDV against RNA viruses has been well characterised over a decade for the coronaviruses SARS-CoV and MERS-CoV as well as for EBOV. The target of RDV is viral RdRP. RDV is a pro-drug of a nucleoside analogue and is converted first to the alanine metabolite, then to the NMP metabolite and finally to the active NTP. NTP is incorporated by RdRP more efficiently into the viral RNA chain than physiological ATP. This leads to a delayed chain-termination after three additional nucleotides have been added, thus inhibiting viral replication. It is believed that these nucleotides provide protection from excision of the incorporated RDV NTP by the proofreading exoribonuclease ExoN.

b) Antiviral activity (*in vitro*, *in vivo*), cytotoxicity and selectivity indexes

For RDV the antiviral activity against the coronaviruses SARS-CoV, MERS-CoV and SARS-CoV-2 had been determined in several *in vitro* and *in vivo* studies. The first *in vitro* antiviral activity study for SARS-CoV-2 were Vero E6 cells and determined a low EC_{50} value and low cytotoxicity resulting in a high selectivity index. Another cell culture to determine antiviral activity were HAE. *In vivo* antiviral activity of RDV against SARS-CoV-2 was demonstrated in rhesus monkeys (NHP).

c) *In vitro* combination activity analysis

Combination activity analysis of RDV another antiviral for the same indication has not been performed due to the lack of other antivirals approved for COVID-19. Once another antiviral is approved such analysis can be performed.

e) Resistance

It is expected that RDV has a quite high genetic barrier to antiviral resistance because of the well-conserved target RdRP. Furthermore, the effect of the proofreading enzyme ExoN is rather low due to the delayed chain termination. Another issue is that mutant SARS-CoV viruses with substitutions at homologous amino acid residues near the RdRP encoding region showed reduction in susceptibility to RDV, but likewise also a reduced viral fitness compared to the wildtype. This is also assumed for SARS-CoV-2, though SARS-CoV-2 resistance to RDV has not yet been assessed.

The guidance recommends the genotypic and phenotypic analysis of mutant viruses with resistance to the antiviral. These analyses have not yet been conducted for mutant SARS-CoV-2 viruses that are resistant to RDV. However, also in clinical practice no occurrence of SARS-CoV-2 strains with reduced susceptibility to RDV have yet been published.

The guidance also recommends the analysis of cross-resistance to other antivirals in the same drug class. As RDV is the first FDA-approved antiviral of its class the investigation of cross-resistance is obsolete to date.

4.5.1.2 Monitoring resistance development

A monitoring plan for the development of resistant viruses in clinical studies is recommended by the guidance. This has not yet been realised for clinical trials with RDV for EBV or COVID-19. This is partly due to the fact that viral loads, as part of the monitoring, were not determined in the context of the clinical trials for COVID-19 and resistance to RDV is not yet known.

4.5.2 FDA guidance on developing drugs for COVID-19

This guidance specifically describes the recommended requirements for clinical phase II and phase III trials to establish safety and efficacy for drugs to treat or prevent COVID-19.

Population

- The guidance recommends to include patients from a range of populations, such as hospitalised patients or patients cared for outpatient. However, the phase III clinical trials with RDV for COVID-19 included only hospitalised patients. Also, FDA approved use of RDV is limited to patients requiring hospitalisation. Partly this is due to the fact that RDV can only be administered IV and the safe administration in a home setting has not been established.
- According to the guidance the severity of COVID-19 in the trial population at baseline should be categorised. All phase III trials with RDV classified the severity of disease according to objective criteria.
- The guidance recommends to include patients with renal or hepatic impairment, patients at high risk of complications, pregnant and lactating women and children. However, no hepatic or renal impairment trial had been conducted at the time of FDA approval of RDV and was therefore addressed as a PMR. PMRs also included the conduct of clinical trials in paediatric patients with COVID-19. A PMC was to collect PK and safety data in pregnant women.

Trial design

- Following the guidance, the trial design should be randomised, placebo-controlled and double-blind and all treatment arms should receive background SOC. The duration should be adequate to evaluate the efficacy endpoints. From the three key phase III trials on which the FDA approval of RDV is based only the ACTT-1 trial meets these rigorous criteria, but did not include background SOC. The other two supportive trials were open-label, of which only the SIMPLE II trial had a SOC control arm. The duration of all three trials was long enough to assess the primary efficacy endpoints: ACTT-1: time to recovery until day 29; SIMPLE I: clinical improvement on day 14; SIMPLE II: odds of improvement of clinical status on day 11.
- Corresponding to the guidance previous nonclinical or clinical evidence can be taken into account to directly start phase II or phase III clinical trials. Also, an adaptive trial design is recommended. Concerning the results of nonclinical trials with RDV for EVD, SARS and MERS were considered and only the specific antiviral activity against SARS-CoV-2 was characterised *in vitro* and *in vivo*. Furthermore, the results of the phase I PK

trials with RDV conducted during the EBV epidemic could be used to plan the RDV phase III trials for COVID-19. The start of these trials could therefore take place at an early stage in the drug development process. Of the three main phase III trials leading to FDA approval of RDV the ACTT-1 trial had an adaptive trial design.

- A data monitoring committee recommended in the guideline was realised for the ACTT-1 trial (Data and Safety Monitoring Board). For the other phase III trials described above no data monitoring committee has been mentioned.

Efficacy endpoints in trials for COVID-19

- Efficacy endpoints are recommended in the guidance to be clinically important outcome measures. The RDV phase III trials for COVID-19 described above use such primary endpoints: clinical improvement (SIMPLE I, RCT in China, SIMPLE II), time to recovery (ACTT-1) and mortality (SOLIDARITY). The time points when to evaluate the endpoints was according to the severity of the disease and type of endpoint.
- The guidance mentions virologic endpoints (e.g., viral load) as secondary endpoint in phase III trials e.g., to evaluate antiviral resistance. Of the RDV phase III trials for COVID-19 mentioned above only the trial in China measured viral load as secondary endpoint.

Safety considerations

- In line with the guidance, AEs should be should be assessed and graded according to a toxicity grading scale and safety assessments be performed according to the risk of the investigated drug. For RDV phase I PK trials after COVID-19 outbreak AEs were evaluated and laboratory abnormalities classified as grade 1 and 2 (such as elevations of ALT/AST levels, reversible prolongation of PT). In the ACTT-1 phase III trial AEs were assessed and the grade determined, e.g., some grade 3 and 4 AEs, such as anaemia or increased ALT/AST occurred. The AE classification applies also to the other RDV phase III trials for COVID-19.

Statistical considerations

- The guidance recommends to perform the primary efficacy analysis in the ITT population. For the 3 key phase III trials for FDA approval of RDV for COVID-19 the primary efficacy analysis was performed in the ITT population.
- In line with the guidance the trial sample size should be large enough to prove safety and efficacy. In the phase III RCT in China the calculated sample size was not reached and thus was statistically underpowered as the trial was stopped prematurely.

4.5.3 FDA guidance on considerations for pre-IND meeting requests for COVID-19 related drugs

This guidance aims to prepare pre-IND meeting requests for COVID-19 related drugs. It summarises the requirements for the preparation of the request by the sponsor.

For RDV it is not published whether a pre-IND meeting request was submitted by the sponsor. However, the FDA assessment of RDV approval mentions that RDV was initially studied under an IND for EVD[61]. This IND was placed on hold after in a clinical trial the RDV arm was terminated early as two other trial drugs were associated with greater survival. Furthermore, a fatal AE of cardiac arrest occurred under RVD that could not be clearly considered unrelated to RVD. A new IND[62] was opened for the treatment of COVID-19 in February 2020. (9)

For confidentiality reasons it has not been published if a pre-IND meeting for the IND for COVID-19 had taken place. It can be assumed that the pre-IND request for the new IND was filed and answered very quickly due to the fact there was a previous IND for EVD with the necessary information. This includes nonclinical and toxicology data. According to the guidance general toxicology studies in two species (at least one nonrodent) are recommended. *In vivo* nonclinical studies with RDV are only possible in NHP models (mainly in rhesus monkeys), but not in rodents. Furthermore, clinical trials for EVD could be referred to: several phase I PK trials during the EVD epidemic and a large phase II-III trial for the IND for EVD, that ended prematurely for the RDV arm (see above). Moreover, a summary

[61] IND 125566
[62] IND 147753

of safety data of these clinical trials could be submitted for the IND for COVID-19. The NIH sponsored ACCT-1 trial reflects the trial design requirements of the guidance.

4.5.4 CTAP program

This FDA program has the aim to ensure that sponsor requests to a new drug proposed for COVID-19 treatment is reviewed by the responsible FDA division. CTAP's successive milestones are the pre-IND meeting, IND filing, issue of EUA, NDA filing, approval.

For RDV for the treatment of COVID-19 all of CTAP's milestones have been reached. However, for the pre-IND meeting and when filing the IND in February 2020 the CTAP program was not yet in place, as it was only initiated end of March 2020. It can be assumed that the remaining milestones for RDV were achieved in the scope of CTAP.

4.6 Drug development of remdesivir for Ebola virus disease: an enhancer for the development for COVID-19?

RDV was identified by screening and demonstrated that it possesses broad-spectrum activity against RNA viruses. The nonclinical development of RDV in the context of EVD was quite advanced. This included the elucidation of the MOA. In fact, nonclinical research has not only been advanced by research of antiviral activity of RDV against EBOV, but also by research of antiviral activity against the coronaviruses SARS-CoV and MERS-CoV. At the onset of the COVID-19 outbreak, antiviral activity against SARS-CoV-2 was first characterised. The animal PK of RDV had been investigated for EVD as well, including the search for the most suitable animal model, the rhesus monkeys. By bridging PK data from rhesus monkeys to humans, the FIH starting dose for clinical trials for EVD was selected. In 2015 an IND application for RDV for the treatment of EVD was filed.
At the onset of the COVID 19 outbreak, antiviral activity against SARS-CoV 2 was first characterised.

RDV was evaluated for EVD in a phase I PK clinical trial healthy volunteers during the 2018 epidemic, investigating single-doses (3-225 mg) or multiple-doses of RDV. The safety of RDV was also assessed in this trial, RDV was well tolerated. Several other phase I PK trials

with RDV were conducted during the EVD epidemic which made only a few new PK studies necessary during the COVID-19 pandemic.

The largest clinical trial for EVD during the 2018 outbreak was a phase II-III trial in a RCT parallel 1:1:1:1 design with 3 treatment groups, including RDV, and one control group. In the interim analysis RDV failed to show clinical benefit as the mortality rate (primary endpoint) was inferior to the other two trial drugs. As a result, the RDV group was terminated. In addition, clinical development of RDV for EVD was subsequently stopped.

Clinical development for COVID-19 was able to proceed from this point, allowing large phase III studies to begin at an early stage during the pandemic. In addition, during clinical development for EBV the formulation of RDV had been optimised and the manufacturing processes had been scaled up.

The tool of drug repurposing has received a significant amount of attention to address the current COVID-19 pandemic. Repurposing an effective small-molecule therapeutic promises the fastest therapeutic means to meet the needs in the pandemic. (5) RDV is a small-molecule drug whose development for the repurposed indication of COVID-19 had been accelerated based on the development for EVD, but also for SARS and MERS. The speed with which RDV has entered clinical drug development had been expedited by the clinical experience in the development for EVD and reflects the need for treatment options in this public health emergency. (5)

5. Expedited approval procedures for remdesivir in the USA and comparison with the approval status in the EU

5.1 Expedited approval procedures in the USA and the EU

The expedited approval pathways in the USA are explained in detail in this section. Only the EMA pendent of the FDA accelerated approval procedure is briefly mentioned. (53)

For serious diseases and unmet medical needs, such as the COVID-19 pandemic, the FDA and EMA have developed multiple mechanisms to expedite both the drug development

process and application review timelines for promising drugs intended to treat such serious disease and unmet medical needs. FDA and EMA allow for more than one of these expedited pathways to be pursued in parallel. (53)

5.1.1 Reduced drug development time

The FDA offers programs during drug development to enable more detailed feedback and closer collaboration between the applicant and the agency. Such programs are Fast-Track Designation and Breakthrough Therapy Designation. (53)

FDA: Fast-track Designation (FTD)

For FTD it is required that the nonclinical and clinical data of a drug indicates substantial improvement in efficacy, safety or diagnosis for a serious condition over existing therapies. FTD is intended to expedite the development of drugs to treat serious conditions and fill an unmet medical need. A condition is assessed as serious if the drug is assumed to have an impact on patient-related factors, such as survival, or the likelihood that the untreated condition, will progress to a more serious one. An example is cancer. Filling an unmet medical need means to provide a therapy where none exists or providing a therapy that may be potentially better than available therapy. If no current therapy to treat or prevent a serious condition exists this unmet need gains weight in the situation of an emerging public health need. Any drug developed to treat or prevent a condition with no current therapy is clearly directed at an unmet need. If available therapies exist, a drug must demonstrate an advantage over existing therapies to be eligible for FTD, such as

- superior efficacy on serious outcomes
- superior safety profile, particularly for serious side effects of an existing therapy

For a drug that receives FTD it is required that its nonclinical or clinical data indicate substantial improvement in efficacy, safety or diagnosis for a serious condition over existing therapies.

A drug with FTD is subject to some or all of the following benefits:

- more frequent meetings with the FDA to ensure FDA's general expectations for drug development are met, e.g., collection of appropriate data for the nonclinical and clini-

cal trials

- more frequent written communication with the FDA about e.g., design of clinical trials
- Rolling review. This means that completed sections of the NDA[63] can be submitted for review by the FDA, rather than waiting until all sections are completed before they can be reviewed. This potentially expedites time to approval.

FTD requests can be initiated at any time during the drug development process, usually they are submitted for the IND. The FDA will decide within 60 days of the request.

FDA: Breakthrough Therapy Designation (BTD)

A drug can qualify for BTD if it is intended to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate "game changing" improvement over existing therapies on one or more clinically significant end points. In contrast to FTD initial clinical evidence is required, whereas FTD may use nonclinical data as evidence.

Examples of clinical evidence that could support BTD:

- If the comparison of the IP to existing therapy demonstrates a substantial benefit on a clinically significant end point.
- If no existing therapy exists, the IP should be compared to placebo/historical control and shows a substantial effect on a clinically meaningful end point.

The FDA can cancel BTD later in drug development if the criteria are no longer met.

Benefits of a BTD include in principle all elements of an FTD. A specific property is that senior FDA staff is involved, together with a cross-disciplinary project lead to provide thorough guidance for the drug development. The request for BTD can be submitted at the time of the IND submission or any time before approval, ideally before the meeting at the end of phase II. The FDA responds within 60 days of the request, as for the FTD. (53)

[63] NDA: data package to obtain a marketing approval for small-molecule drugs the data submitted to the FDA. The equivalent for biologics is a BLA. (53) Since RDV is subject to an NDA, for the purpose of simplicity only "NDA" is mentioned in this section and not "BLA", although it mostly concerns both.

EMA: PRIority MEdicines (PRIME) Designation

Eligibility criteria for the PRIME designation are that the drug under development shows the potential to target a condition with an unmet medical need and will bring a major therapeutic advantage to patients, e.g., improved morbidity or mortality of the disease. (53)

The main benefits of the PRIME scheme are:

- Early appointment of a rapporteur during drug development to guide the applicant. In a standard Marketing Authorisation Application (MAA) the rapporteur is assigned later, a few months before submission.
- Meetings with the rapporteur and EMA experts to discuss the development plan
- Overall guidance, including scientific advice from the EMA and experts at drug development milestones. (53)

5.1.2 Decreasing application review time

FDA: Priority review

After the NDA (BLA) has been submitted the priority review pathway can reduce the review time by FDA. The standard review time is 10 months for an NDA (BLA) (including a 60-day filing review period). For a priority review the goal is to reduce the review time to 6 months. The qualifying criteria for a drug are that it is intended to treat or prevent a serious condition and can provide a significant improvement in efficacy or safety. A "significant improvement" can include:

- evidence of increased efficacy in treatment, prevention, or diagnosis of a condition.
- evidence of substantial reduction of a treatment limiting adverse reaction.

If there is a drug already approved for the same indication, the NDA of the IP should provide data from a clinical trial to demonstrate superiority in either safety or effectiveness to support a significant improvement over the approved drug.

After receiving a request for priority review with the filing of an NDA, the FDA will decide on the request within 14 days of the initial 60-day filing review period of the NDA. After granting priority review it can be taken back again (e.g., due to FDA queries), so that standard review timelines apply. (53)

Additionally, to drugs qualifying to the above-mentioned criteria of this pathway, further mechanisms allow for priority review, including:

- an application for a drug that has been designated as a qualified infectious disease product.
- an application for a drug submitted with a priority review voucher. Priority review vouchers are obtained at a previous NDA (BLA) approval for a drug whose indication is a rare paediatric disease. The voucher may be used for any subsequent application to obtain priority review or be even be sold to another company. (53)

EMA: Accelerated assessment

The accelerated procedure reduces the 210-day review time of a standard procedure by 60 days to a 150-day review time. To qualify for accelerated assessment, the drug must represent a "major public health interest".

5.1.3 Preliminary approval pending additional data

FDA: Accelerated Approval

In case only preliminary data can be provided for an NDA (BLA) the accelerated approval is an option to receive an approval valid for a limited time. (53)

Qualifying criteria for this pathway are that the drug is

1) meant to treat a serious condition and
2) should provide a meaningful advantage over available therapies and
3) demonstrate an effect on a surrogate end point or on an intermediate clinical end point[64] and are both reasonably likely to predict clinical benefit. (53)

Drugs granted accelerated approval must meet the same statutory requirements for safety and efficacy as for the standard approval pathway.

Additional data, such as post-marketing confirmatory trials, are required after approval to verify the anticipated clinical benefit. If the benefit is confirmed the accelerated approval

[64] Intermediate clinical end point: can be measured earlier than e.g., mortality and irreversible morbidity. (53)

can be converted to a “full approval.” If these additional data do not confirm the previously assumed benefit, approval may be withdrawn. The confirmatory trial population is typically the same population studied to support accelerated approval.

The applicant should discuss the possibility of accelerated approval with the FDA during drug development. This should include the planned surrogate or intermediate end point as well as the type of confirmatory trials proposed. Confirmatory trials normally already have started when applying for accelerated approval. If these additional data do not confirm the previously assumed benefit, FDA may withdraw the accelerated approval of a drug or indication. (53)

EMA: Conditional Approval

The pathway of conditional approval enables an approval based on less clinical data than for standard approval. It applies to drugs that are new molecular entities and have the potential to address an unmet medical need.

This pathway is applicable for drugs that:

- are for the treatment of seriously debilitating or life-threatening diseases, or
- that may be used in public health emergency situations, or
- are for rare diseases. (53,54)

The following qualifying criteria must all be met:

- The benefit to public health of the drug’s availability outweighs the potential risks of limited clinical data.
- It is likely that more comprehensive data will be available later.
- The drug fulfils an unmet medical need. (53,54)

The key aspect of conditional approval is that the applicant commits to “Specific Obligations”. These are mandatory post-marketing requirements to be fulfilled within specified timelines. These requirements are for example the assessment of additional clinical end points of a trial. A conditional approval is only valid for 1 year. Each year, the applicant requests the renewal of the conditional approval and submits the data associated with the specific obligations. The CHMP assesses the progress on the specific obligations and

whether the benefit/risk ratio remains positive; otherwise, the approval can be withdrawn. When all specific obligations are fulfilled the conditional approval is converted to a standard MA. (53,54)

5.2 US expedited approval procedures and programs applied to remdesivir for COVID-19

5.2.1 FDA regulatory milestones for the expedited approval of RDV for COVID-19

The following milestone regulatory events including expedited approval mechanisms led to approval of RDV for the treatment of COVID-19:

January 2020: Expanded access for RDV

February 2020: IND for RDV for the treatment of COVID-19 filed

26 March 2020: Fast-track designation granted

06 April 2020: Rolling review approved of

01 May 2020: EUA granted

10 August 2020: Submission of the NDA; grant of priority review

28 August 2020: Revision of the EUA

22 October 2020: Approval of Veklury (RDV)

22 October 2020: The EUA for Veklury continues and was revised (9,52)

19 November 2020: EUA issued for the combination therapy of RDV and baricitinib[65] (52)

FDA approval of RDV

RDV is approved for adults and paediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalisation. (9,43,44,47,49,50)
For patients who do not need invasive mechanical ventilation or ECMO a 5-day course of RDV is recommended, which can be extended to 10 days. For patients who need invasive mechanical ventilation or ECMO a 10-day course is recommended.

[65] For the treatment of suspected or laboratory confirmed COVID 19 in hospitalised adults and paediatric patients (2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO). (52)

EUA for RDV revised twice to date

The EUA for RDV was first issued on 01 May 2020 and was a result of the interim analysis of the ACTT-1 trial. It was issued for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalised adult and paediatric patients with severe disease.[66] (50,52). FDA revised the EUA on 28 August 2020 EUA by broadening the scope of its authorised uses and including all hospitalised adult and paediatric patients, irrespective of their severity of disease. This decision was mainly based on clinical data that have become available since the original issuance of the EUA. (50,52) With the approval of Veklury the EUA still continues, but was changed again. This current EUA is issued for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalised paediatric patients weighing 3.5 kg to less than 40 kg or hospitalised paediatric patients less than 12 years of age weighing at least 3.5 kg. For the current EUA the indications that have been approved were removed i.e., hospitalised adults and paediatric patients (12 years and older and weighing at least 40 kg). The approval and the current EUA considered together cover in total adults and paediatric patients weighing at least 3.5 kg or paediatric patients less than 12 years of age weighing at least 3.5 kg. In summary, the EUA was issued and twice revised based on new clinical data or due to the approval of RDV. (50,52)

5.2.2 Expanded Access, EUA and FDA approval

Expanded Access

Besides the EUA another pathway for the early access to investigational drugs is the "expanded access" for drugs. Expanded access is individually issued for a patient, whereas the EUA applies to a public health emergency. Patients receiving drugs under expanded access must have a serious or life-threatening disease or condition, for which no alternative treatment is available, they cannot take part in clinical trials. When an EUA is issued for the respective drug the expanded access destination is terminated. The expanded access for RDV existed from end of January 2020 until the EUA on 01 May 2020. (10,55)

EUA

For an EUA the HHS Secretary has to declare a public health emergency. For COVID-19

[66] Severe disease was defined as patients with low blood oxygen levels or requiring supple-mental oxygen or invasive mechanical ventilation.

public health emergency was declared on 31 January 2020.

To issue an EUA for drug that is not approved, the FDA must assess all of the following:

- that the drug *may* be effective in protecting the nation's public health by diagnosing, treating, or preventing a serious or life-threatening disease or condition or caused by a chemical, biological, radiological, or nuclear agent.
- that there is a positive benefit/risk ratio for the drug
- that there are no adequate, approved, and available alternatives

EUAs only remains effective only as long as the grounds for the EUA exist or the drug has not been approved. (50,54)

FDA approval

During drug development first an IND for the investigational drug is filed. When the non-clinical and clinical data package is ready for submission an NDA is filed to apply for the marketing approval of this drug. By approving an NDA, FDA reviewers assess that the drug is safe and effective for its labelled use, the benefits of the drug outweigh the risks and the drug manufacturing methods have the required quality. The NDA approval requires substantial evidence of effectiveness, more than is required for an EUA. (50)

5.3 EU expedited approval procedures applied to remdesivir for COVID-19

This section is limited to the main regulatory steps that led to the approval of RDV in the EU. The EU has no formal EUA as the USA, but it has several tools that can be used in the event of a public health crisis. (54)

Compassionate Use

Initially RDV was available in the EU by compassionate use from 03 April 2020 until approval. This program is comparable to the US expanded access as for both the use of an unapproved drug is allowed, they are for life-threatening or long-lasting diseases for whom no approved drug is available and for patients who cannot enter a clinical trial. Compassionate use is intended for a group of patients unlike the expanded access. A compassionate use opinion may be requested by any EU Member State for drugs being

investigated in clinical trials or for which a MAA has been submitted. When a positive CHMP opinion has been issued each Member State is free to make use of it at national level[67]. (54,56)

Conditional Approval

The conditional approval decision for Veklury was granted on 03 July 2020 (Decision) following the positive CHMP Opinion (25 June 2020). Very many specific obligations in terms of quality, safety, and efficacy were imposed to the applicant at approval, e.g., safety monitoring according to a Risk Management Plan. (54)

6. Regulatory learnings from the expedited approval of remdesivir in the USA and future aspects

In the COVID-19 pandemic the USA had regulatory tools in place to ensure patients have early access to antiviral treatment. This concerns antivirals under development that have not yet been approved, as well as regulatory pathways for the expedited approval of such antivirals.

RDV was the first approved drug in the USA. On the basis of RDV, one can recognise the regulatory tools that have been used for early access before its approval and the accelerated approval procedures since the beginning of the pandemic.

RDV was accessible very early to individual patients through the Expanded Access program after it had been declared a public health emergency on 31 January 2020.

The regulatory tool of Expanded Access was replaced by an EUA on 1 May 2020. The reason for issuing the EUA were the results of a faster recovery time in patients with mild to severe COVID-19 after the interim analysis of the ACTT-1 trial. The regulatory barriers for an EUA are considerably lower than for the approval of an NDA. Furthermore, the EUA is flexible and was adapted several times for RDV according to new information, e.g., from clinical trials, and according to the regulatory environment, such as approval of RDV.

[67] Germany was one of the countries that made use of the Compassionate Use opinion. (56)

The drug development of RDV in the USA was enhanced by regulatory guidances and a program:

The FDA guidance on antiviral drug development from 2006 the guidance clarifies the objectives and conditions for nonclinical and clinical trials of antivirals. (21) In May 2020 two further FDA guidances were issued, one on development of drug for COVID-19 and one on considerations for pre-IND meeting requests for COVID-19 related drugs. (26,28) These guidances have specified the FDA's expectations for the development of COVID-19 drugs and enabled the early exchange of information between the applicant and the FDA. This enables efficient and rapid drug development.

The regulatory program CTAP offers a rapid review and early discussion between the FDA and drug developer to achieve the milestones Pre-IND meeting, IND filing, EUA, NDA filing. For RDV it can be assumed that only the milestones EUA and NDA were achieved within the frame of CTAP as the other milestones for RDV had been reached before CTAP started (end of March 2020).

The following expedited regulatory pathways came into effect for RDV:

RDV received fast-track designation. This meant more frequent meetings and written communication with the FDA. A rolling review is part of the fast-track designation, which allows to submit NDA sections piece by piece to the FDA for review. When the remaining NDA sections are filed FDA has reviewed most NDA sections already. When the NDA was submitted it also received priority review designation, which expedited the FDA review time. As a result of these expediting mechanisms the NDA was approved slightly less than 3 months after the last NDA section was submitted. (47)

When comparing early access to drugs not yet approved and expedited approval pathways of drugs in the USA and EU there are several similar mechanisms (see *Table 3*).

Table 3: Early access to drugs not yet approved and expedited approval pathways of drugs in the USA and EU

	USA		EU
Access to investigational drugs in a public health emergency			
	Expanded access pathway	EUA	Compassionate use
Expedited approval procedures of drugs for the needs in a public health emergency			
Reduced drug development time	Fast-track designation	Breakthrough therapy Des-ignation	PRIME
Decreased authority review time			
	Priority review		Accelerated assessment
Preliminary approval subject to additional data			
	Accelerated approval		Conditional approval

Besides these accelerated mechanisms specific to the US and the EU drug development and approval could even further expedited by more interaction between the FDA and EMA. This could be regular meetings between the FDA and EMA. Another possibility is the exchange of scientific data on drugs in development between the authorities. Exchange at different levels between the authorities would be beneficial. The intensive exchange between the authorities would save time and resources.

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Freiburg,

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Francesca Haaf