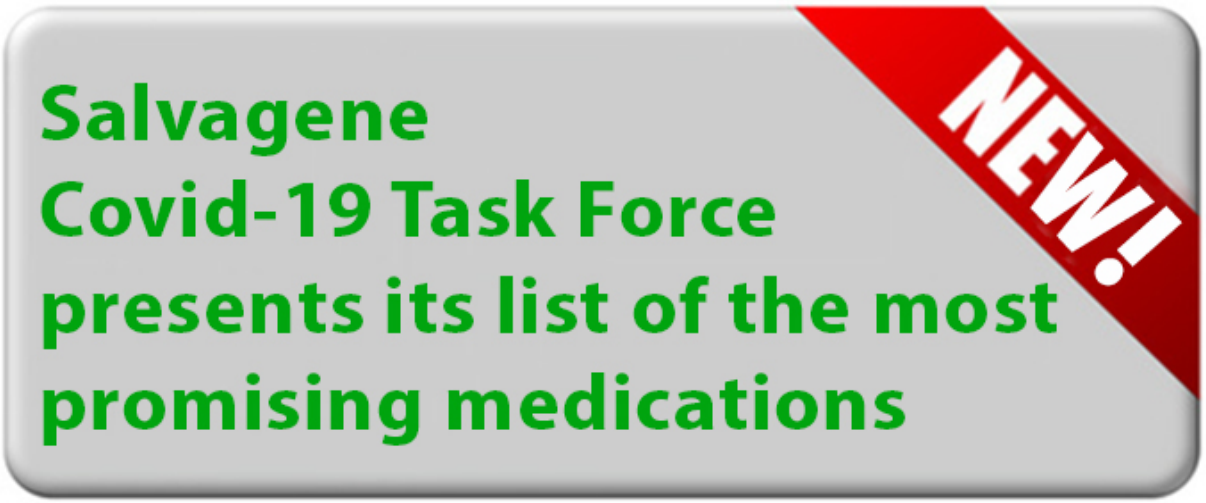
Salvagene GROUP

Business Unit: SARS-CoV-2 Task Force
Keynote: #17

April 2020



Dear Premium Customers,

Today: Remdesivir

We recently reported on the best prospects for medications and vaccines from 100 ongoing projects (See Keynote 15).

At the moment, we estimate the earliest we can hope for a vaccine against the SARS-CoV-2 virus is around the first or second quarter of 2021. Even then, it will still not be really clear to what extent the active ingredient works for everyone, as the speed of mutation is currently accelerating, so that a vaccine may only have a limited effect, as is the case for those developed to combat influenza viruses.

Furthermore, the extent to which the much-debated "herd immunity" will actually apply is purely hypothetical; our antibody monitoring has cast some doubt on the length of time for which antibodies remain effective.

That leaves two courses of action:

1. Optimizing Health and systematically and continuously eliminate all risk factors for a medium and severe infection, e.g. by means of our new Salvagene Covid-19 Immunization Program.

2. To identify medications that work effectively to mitigate severe and moderate Covid-19 symp

The Salvagene Covid-19 Task Force has taken a look at almost 100 ongoing research projects into substances that might prove effective against Covid-19. To our knowledge, there are more than 300 studies that are either underway or in preparation. The focus here is primarily on drugs that have already been used to treat other diseases, such as malaria, hepatitis or multiple sclerosis. The advantage of this "repurposing" – i.e. the adoption of substances for a different purpose – is that, in the best-case scenario, they do not have to undergo costly and time-consuming testing procedures. Active substances that have already been thoroughly researched can proceed to the clinical trial phase sooner and thus be approved more quickly.

In parallel, completely new substances are also being researched, with reference also being made to findings from the related SARS coronavirus outbreak of 2002/03. Members of our Task Force team are in direct contact with the project groups.

We now want to present what we consider to be one of the most promising candidates in terms of rapid availability. And its Remdesivir.

It is currently being tested on thousands of patients worldwide, including in Germany which is where the most extensive testing is taking place and where we have direct access to the projects.

The expectations are high, very high indeed. As our Canadian colleague and epidemiologist Bruce Aylward put it at a WHO press conference in Beijing: “There is currently only one drug that we believe may actually work. And that is Remdesivir.”

At that time, the corona epidemic in China had just reached its peak. Bruce Aylward is advisor to the Director-General of the World Health Organization (WHO) and head of the WHO and Chinese joint operations. We are not the only researchers who are currently pinning great hopes on the substance.

STAT, a website specializing in health issues, reported on Thursday that the drug had performed well on corona patients in a Chicago hospital participating in clinical trials. However, manufacturer Gilead said the full data still had to be analyzed before any conclusions could be drawn.

On Friday, scientists working for the U.S. government reported on a small experiment on twelve monkeys intentionally infected with SARS-CoV-2. The state of health of the monkeys treated with remdesivir had already improved significantly after twelve hours. However, the preliminary study results have not yet been independently assessed.

“For me, remdesivir is rightly one of the top candidates,” says Stefan Schreiber, Director at the University Medical Center Schleswig-Holstein (UKSH). He is currently testing remdesivir on Covid-19 patients at his clinic. “The substance is well tolerated, has a good profile for removal of the virus and has shown good efficacy in the first reported Covid-19 treatments.”

Marylyn Addo is also testing remdesivir on patients at the University Medical Center Hamburg-Eppendorf (UKE), and she too

is optimistic: “I also regard remdesivir as a promising substance, but it has to be subjected to critical testing.”

Scientists around the world are desperately searching for a medication to treat the potentially fatal lung disease Covid-19. Originally developed to combat Ebola, remdesivir, is one of several candidates currently being tested on thousands of patients, including the HIV drug Kaletra and the anti-malaria drug hydroxychloroquine. The first results should be available as early as May.

Unlike a vaccine, which is not on the horizon until next year at the very earliest, remdesivir cannot prevent infection with the novel coronavirus. But it can stop its proliferation in the body and take away the terror of the disease. Fewer people would die, recovering patients would be discharged from hospitals more quickly, the pressure on the health care system would be relieved, the lockdowns could be eased, and the economy could start up again.

But all of that is still a long way off. Remdesivir proved to be a disappointment against Ebola and looked like it was heading for oblivion. But now we hope that it might be successful in combating SARS-CoV-2.

What is Remdesivir?

Remdesivir was developed by the American pharmaceutical company Gilead Sciences in the 2010s – initially under the name GS-5374 – in the search for a substance to combat the Ebola virus. At first, hopes were high. Experiments on animals with remdesivir in 2016 produced promising results, and researchers were able to cure Ebola-infected rhesus monkeys with it.

But when it came to testing on humans, remdesivir failed. In the first and only clinical phase 3 study (2018/2019), remdesivir was tested on 175 Ebola patients in the Democratic Republic of Congo. Three other patient groups received different medicines.

The result was that 93 of the 175 Ebola patients had died by the end of the 28-day trial period. Two other antibody preparations achieved a better effect than remdesivir, and treatment with remdesivir was stopped for ethical reasons. Its career as a potential cure for Ebola seemed to be over.

But remdesivir was not only trialed for effectiveness against the Ebola virus. A few years earlier, scientists had discovered in laboratory experiments that it could combat a whole range of other viruses, including Lassa, Marburg and also various coronaviruses, for example the first SARS coronavirus and the MERS virus.

As early as January 2017, a research team led by the American epidemiologist Timothy Sheahan wrote about remdesivir with prophetic foresight: “Given its versatility, this antiviral substance could be used to prevent a future coronavirus outbreak from getting out of control.”

In January 2020, attention once again turned to remdesivir as Chinese scientists began testing it as a remedy for the novel coronavirus SARS-CoV-2. With some degree of success. But only on cell cultures in the laboratory.

How does it work?

Remdesivir is a so-called nucleotide analog. It is very similar to one of the building blocks that make up the genetic molecule RNA.

Coronaviruses are made up of RNA. This molecule contains the complete construction manual for a new virus, including a copying machine, the enzyme RNA polymerase. When the coronavirus infects a body cell, the machinery inside the cell reads the viral genome and builds new viral proteins as well as the RNA polymerase. The latter sets about its work and begins to produce many copies of the viral RNA. New coronaviruses are manufactured; they leave the cell and infect others – a chain reaction.

This is where the nucleotide analog remdesivir comes into play. It presents itself to the RNA polymerase as a deceptively genuine RNA building block. But as soon as the enzyme incorporates it into the RNA strand, the copying process stops, the duplication of the coronaviruses comes to a standstill and the chain reaction is halted.

Remdesivir works in all viruses that use RNA as genetic material and multiply by means of RNA polymerase, including Ebola, Marburg virus, Lassa, Nipah, Hendra, Junin, Chikungunya.

In laboratory tests, remdesivir has already shown good efficacy against the novel coronavirus SARS-CoV-2. Next comes the ultimate test – on humans.

Does it help in the fight against Covid-19?

The first American Covid-19 case was a 35-year-old patient who was admitted to a hospital in Snohomish County, Washington State, on 19th January 2020 with a fever and cough. The man had returned from Wuhan, the epicenter of the Corona pandemic. On 20th January, he tested positive for SARS-CoV-2. Within a few days, he developed severe pneumonia, his oxygen saturation dropped to 90 percent and he had to be ventilated. His doctors take up the narrative in the New England Journal of Medicine (NEJM).

The physicians decided to administer remdesivir on the grounds of "compassionate use", i.e. the use of as yet unapproved medicines with seriously ill patients who could otherwise not be treated adequately.

Quoting from the doctors' report: "Intravenous treatment with remdesivir was started on Day 11 of the illness. On Day 12, his condition improved, ventilation was stopped, and oxygen saturation rose to 94 to 96 percent."

This was the first documented Covid-19 case in which treatment with remdesivir was successful. In a summary that has just been published in the New England Journal of Medicine, doctors from different countries report 53 further cases in which Covid-19 patients were given remdesivir, including two cases in Germany overseen by Torsten Feldt at the University Hospital in Düsseldorf. Like Marylyn Addo in Hamburg and Stefan Schreiber in Kiel, Feldt is currently testing remdesivir on Covid-19 patients.

40 of the patients in the NEJM report received remdesivir intravenously for ten days, ten for five to nine days and three for less than five days. Among the patients were many elderly people – the average age was 64 years (14 were under 50 years, 21 between 50 and 70 years, 18 over 70 years old). Stefan Schreiber, head of the remdesivir study at the University Medical Center Schleswig-Holstein, is favorably impressed: "The report in the NEJM shows quite a lot of positive progressions."

The net result: in 36 patients, their condition improved as a result of the treatment, in eight cases it worsened, and in another eight it remained unchanged. The doctors make the point that, of the 30 patients who had to be intubated, more than half could subsequently be extubated. Seven patients died despite being treated with remdesivir. The mortality rate among Covid-19 patients treated with remdesivir was therefore 13 percent.

By comparison, of 1,591 Covid-19 patients admitted to hospital in Lombardy, recently compiled statistics show that, on average, one in four died (26 percent). The mortality rate increases with age: in the 64+ age group, the Italian scientists report a mortality rate of 36 percent. However, the mortality rate varies from country to country. In Germany, for example, the Robert Koch Institute states that "people over 80 years have a mortality rate of >15%.".

This is only a preliminary round-up of cases from different countries and not a properly randomized study with control group. To prove the effectiveness of a therapy or a drug, larger test groups are necessary. The more closely standards are complied with, the more reliable a study will be, i.e. researchers randomly assign volunteers to two groups (without the doctor or patient knowing who belongs to which); the trial group then receives the drug or therapy to be tested while the control group receives a placebo or the standard therapy.

What other studies are currently underway?

In the framework of the Solidarity program, the WHO is currently testing the most promising anti-Covid-19 drugs on thousands of patients worldwide – including remdesivir.

The EU is testing the same substances in the Discovery study.

In addition, the manufacturer of remdesivir – the pharmaceutical company Gilead – has initiated two large multinational studies worldwide in which remdesivir is being tested on 1,600 patients with moderate Covid-19 symptoms and 2,400 patients with severe Covid-19 symptoms. German hospitals are also involved in these studies.

Torsten Feldt, who is leading the study at the University Hospital of Düsseldorf, explains: "The study involves patients with severe Covid-19 symptoms. They are allocated to two groups, one of which will receive remdesivir for five days, and the other for ten days. Patients with moderate symptoms will be divided into three groups: five days of remdesivir, ten days of remdesivir or standard therapy."

The dosage is 200 milligrams on Day 1, then 100 milligrams daily. After 14 days, the patient's health is assessed on a seven-point scale ranging from 1 (death) to 7 (discharge).

All patients receiving the therapy are doing so on a voluntary basis, says Torsten Feldt. "We provide comprehensive information to the patients, informing them that it is an experimental therapy. It is important that the patients understand this, otherwise we cannot include them in the study."

What side effects does Remdesivir have?

In the NEJM summary of the 53 Covid-19 cases treated with remdesivir, 60 percent of patients displayed side-effects, the most common of which were an increase in liver enzymes, diarrhea, skin rash, kidney failure and/or a drop in blood pressure.

23 percent of patients treated with remdesivir had more serious side-effects, including multiorgan failure, septic shock, kidney damage and/or a drop in blood pressure.

Marylyn Addo reports on her patients treated at the University Medical Center Hamburg-Eppendorf: "The drug has been well tolerated so far. We have not yet observed any serious side-effects." Torsten Feldt, too, has mostly seen only mild to moderate increases in liver and kidney complications in his

patients in Düsseldorf. “But these disappear again after discontinuing remdesivir. However, we also know that Covid-19 itself causes this effect, so that it has been difficult so far to determine how much of what we see is down to remdesivir and how much to Covid-19. The randomized trials that are currently underway are also important in this regard.”

Initial results from Germany

“There have been some very positive developments,” reports Marylyn Addo from the University Medical Center Hamburg-Eppendorf. “But, of course, we are seeing a whole spectrum. We’ll have to wait and see.”

Feldt, Addo and Schreiber expect first results in May. If all goes well, remdesivir could then receive so-called emergency approval and be used to treat many more Covid-19 patients.

Gilead has already ramped up its production of remdesivir because is a difficult drug to manufacture. The company promises to provide 140,000 doses by the end of May, and one million by the end of the year.

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