Public Information

AMAL Therapeutics S.A.

Study Title

An Open-Label, Multicenter, Non-Randomized, Dose-Confirmation and Cohort-Expansion Phase 1b Study to Evaluate the Safety, Tolerability, and Anti-Tumor Activity of ATP128, VSV-GP128 and BI 754091, in Patients with Stage IV Colorectal Cancer

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1 General Information

1.1 Description of the Genetically Modified Organism

1.1.1 Introduction

In this clinical trial, a candidate viral vaccine is being tested to treat stage IV colorectal cancer as part of a heterologous prime-boost vaccination regimen. The viral vaccine, called VSV-GP128, is given by a single injection into the bloodstream (i.v., or intravenous) alongside other cancer treatments.

1.1.2 Description of the GMO

VSV-GP128 is a recombinant Vesicular Stomatitis Virus (VSV), classified as a live-attenuated virus. VSV and its close relatives occur naturally in South and North America but VSV-GP128 has been genetically modified from such a virus for improved safety and to act as a vaccine.

The unmodified, naturally occurring (or wild type) -VSV, mainly infects livestock such as cattle, horses, and swine, although it is also able to infect other species. The virus is classified as being arthropod-borne, as it is spread between hosts through the bite of insects, although transmission can also occur directly from cuts or lesions if the area is infected and a large amount of virus is present.

VSV is generally not considered to be a human pathogen, and there are no reports of it being spread directly from human to human. However, it has been known to affect humans that are in close contact with animals, such as veterinarians or livestock handlers. In these situations, VSV can cause a flu-like illness.

The natural glycoprotein (G) on the virus surface which allows wild-type (wt)VSV to attach to and enter host cells, among them neurons and blood cells, has been modified in VSV-GP128, to minimize the potential of neurotoxicity for humans and skin disease in animals. Therefore, the risk of it being spread between animal hosts is very low (see 2.1).

In addition, VSV-GP128 has been engineered to contain cancer antigens, which help it induce an immune response against colorectal tumour cells.

1.2 Nature and Purpose of the intended trial

The proposed study will be conducted with a total of approximately 96 patients who have been diagnosed with Stage IV colorectal cancer of which 45 are planned to receive the viral vaccine, VSV-GP128. The study start in Belgium is expected for Q1 2022 (“First patient in” in Belgium) and expected to last until Q4 2023 (“Last patient last visit). The clinical sites in Belgium are “University Hospital Antwerp” (UZA) and “University Hospital Leuven” (UZL). Approximately 10 patients are expected to be enrolled in the viral vaccine cohorts in Belgium.

Another related cancer vaccine, (ATP128), is already being tested in combination with an antibody which enhances the immune response to attack the cancer in the clinical trial KISIMA-01 currently running in Belgium, Switzerland, and in the USA. Data from tests in animal models

show that the combined use of ATP128 and VSV-GP128 will increase the immune responses against colorectal cancer. The patients for the amended clinical trial KISIMA-01 involving VSV-GP128 will be stage IV colorectal cancer patients in a maintenance setting after a first line of systemic therapy or with a liver-limited disease eligible for liver surgery.

The main purpose of this trial is to determine the safety, tolerability, and efficacy (anti-tumour activity) of the combined therapies. Patients will be given a single intravenous (iv) injection of VSV-GP128 on Day 15. After injection, patients will be observed at the hospital for 8 hours, after which they can go home, and are advised to follow biosafety measures for the next 7 days.

2 Research & Development Activities

2.1 Previous Development Activities

Neither VSV-GP128 nor the highly similar virus VSV-GP which does not contain the cancer antigens; have been previously used as a treatment in humans, meaning this will be a First-In-Human, or FIH, clinical trial. Previous research and development of the therapy was performed in animal studies. These studies looked both at the effectiveness of VSV-GP128 as a cancer therapy, and at the safety for using it.

To understand and exclude the risk of VSV-GP128 spreading into the environment, different animal species (pigs, rabbits, dogs, mice and monkeys) were used. When excess virus is released from an animal (or a human) after infection, for example in the saliva, blood, or urine, it is known as shedding. Looking at the patterns/amount of shedding from animals that have been intentionally infected with VSV-GP128 or VSV-GP, can give an idea of the risk of human patients who have received this treatment spreading the virus either to other people or into the environment. Neither for VSV-GP128 nor VSV-GP shedding of infectious material was found in urine, feces or saliva. This indicates that the potential for transmission of VSV-GP128 is very low.

2.2 Future Activities

Depending on the results of the current study, and particularly outcomes from safety, tolerability and efficacy criteria, further clinical studies may be planned.

2.3 Benefits

Colorectal cancer is the fourth most common type of cancer in Belgium, with an occurrence of around 35.5 cases per 100,000 people (WHO GLOBOCAN database). Stage IV (metastatic) colorectal cancer has a poor prognosis, with a five-year survival rate of only around 14% globally, and most of the current treatment options being palliative rather than curative. AMAL Therapeutics believes that the promising results from their non-clinical programme factored with the high unmet clinical need, support the initiation of a clinical trial with VSV-GP128 in patients who have been diagnosed with Stage IV colorectal cancer. The administration of VSV-GP128 may drive an anti-tumour response or a disease stabilization and possibly improve the survival of patients with stage IV colorectal cancer.

2.4 Risks

As VSV-GP128 is a genetically modified microorganism (GMO), a detailed environmental risk assessment was performed in addition to the standard risk assessment for clinical studies. The main consideration is the risk that VSV-GP128 could be transferred to other people or to livestock. It was also assessed whether there is a risk of transfer of genetic material between VSV-GP128 and either another virus or the human genome. Based on the arguments below, this risk is considered to be negligible.

3 Containment, Control, & Follow-up measures

3.1 Control of the GMO

During the clinical trial which will take place in Belgium at two clinical sites (University Hospitals Leuven and Antwerp), different measures will be put in place to minimise the possibility of VSV-GP128 being transmitted to other people or into the surrounding environment. Detailed instruction including precautions and risk avoiding measures will be provided to the Health Care professionals and the patients.

The VSV-GP128 is injected intravenously which makes the occurrence of significant leakage from the injection site unlikely.

During administration of the treatment, all medical personnel will wear protective equipment, and the syringes for injection will be prepared inside a sterile Biosafety Cabinet. When the syringes are being moved outside of the cabinet, they will be kept in an impermeable container. These measures will reduce the chance of accidental exposure to VSV-GP128.

During their treatment with VSV-GP128, patients' movements around the clinical site will be reduced to the minimum necessary. Whenever the patients do need to leave their room, they will be required to wear a surgical grade mask and to make sure the injection site is covered with a dressing. After the patient is discharged, any potentially contaminated surfaces, such as the furniture in their room, will be thoroughly disinfected. Although VSV has the potential to persist on surfaces for up to 48 hours, temperature, sunlight and disinfectants can easily inactivate it, and reduce possible sources of transmission.

Patients will also be given biosafety instructions to be followed for 7 days after treatment. These include ensuring the injection site is covered with an airtight dressing for at least two days, to collect any trial waste (e.g. plasters) to be disposed of correctly, to reduce close contact with other people, particularly young children, pregnant women, and those who may be immunocompromised, and to not come into contact with livestock.

The safety measures described in 3.1 and 3.2, and the inability of the virus to survive for long outside of a host, will also reduce the chance that humans other than the patients in the trial will have direct contact with VSV-GP128.

3.2 Destruction of the GMO-containing material

All materials that patients have contact with will be handled as though they are potentially infected. These materials will be decontaminated either by steam sterilization, chemical

disinfection and/or incineration. Any needles or sharp objects will be stored in dedicated waste containers before disposal. The disposal of all samples/materials will be carried out according to the waste management rules and local regulations of each clinical site.

3.3 Emergencies

Emergencies, including accidental release into the environment of the VSV-GP128 will be handled according to clinical site procedures. If there is a case of self-administration through a needle-stick injury by medical personnel, the area of the injury will be thoroughly disinfected, and again local procedure at the clinical site will be followed.

3.4 Genetic Stability of the GMO

VSV-GP128 is a single-stranded RNA virus, which does not use a DNA intermediate to replicate. It also replicates in the cytoplasm, which means it does not come into close contact with the human host DNA. Therefore, the risk of genes being transferred from the virus to the human genome is negligible. The VSV-GP128 genome is also tightly bound to a structure called a nucleocapsid, and is thus unlikely to come into contact with or exchange genetic information with other viruses.

3.5 Potential consequences of transmission

Humans aren't considered a natural host for VSV, and transmission of even the wt-VSV from animal to humans is rare. The likelihood of transmission of VSV-GP128 is very low, because even in the natural hosts of wt-VSV there was no transmission of VSV-GP between animals. However, in case of accidental exposure, humans could develop flu-like symptoms.

All patients will be advised to avoid contact with children, pregnant women, and immunocompromised people during treatment until clinical shedding data is available.

To date, there is a limited number of sporadic cases of VSV-induced neurological alteration reported among children: 1 case of VSV-associated encephalitis and 3 more cases when children manifested with neurological symptoms.

Regarding the risk of transmitting the disease to animals and in particular livestock, animal studies showing very low risk of shedding and lack of disease in pigs suggest that this risk is also very low.

Despite the low risk, the risk management measures described above will be implemented during the planned clinical trial to limit exposure of VSV-GP128 to the fullest extent possible.

4 Definitions

Word	Definition
VSV-GP128	The viral cancer vaccine that will be tested in this trial
VSV-GP	A highly similar modified VSV virus which VSV-GP128 is based on
Wild type (wt)-VSV	The naturally occurring form of the virus
Shedding	The release of the tested virus through body secretions, excretions, or body surface lesions
Arthropod	A group of invertebrates that includes insects
Nucleocapsid	The protein shell of a virus, which contains its genetic material

5 Contact Details

Please contact us at the address below if you have any comments regarding this public record or our activities, or if you would like to receive additional information about this deliberate release.

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