PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a)	Member State of notification	Belgium
(b)	Notification number	B/BE/21/BVW4
(c)	Date of acknowledgement of notification	30/09/2021
(d)	Title of the project	

The clinical study to be conducted with VSV-GP128 is entitled:
"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"

(e) Proposed period of release

Q1 2022 – Q4 2023

2. Notifier

Name of institution or company:
AMAL Therapeutics S.A.
Avenue de la Roseraie 64
1205 Geneva
Switzerland

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid	(.)
RNA virus	(X)
DNA virus	(.)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)

specify phylum, class

(b) Identity of the GMO (genus and species)

Genus: Vesiculovirus
Species: Vesicular stomatitis virus

(c) Genetic stability – according to Annex IIIa, II, A(10)

The clinical vector is genetically stable.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes (X) No (.)

If yes, insert the country code(s) DE

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes (.) No (X)

If yes:

- Member State of notification …
- Notification number B/../../…

Please use the following country codes:
Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (X) No (.)

If yes:

- Member State of notification USA
- Notification number IND 027681

7. Summary of the potential environmental impact of the release of the GMOs.

No environmental impact is foreseen. Based on the extensive non-clinical studies performed with VSV-GP128 candidate viral therapeutic vaccine and a highly similar virus, VSV-GP in the most susceptible species naturally affected by the wild-type VSV virus, no untoward effects are expected in humans. Additionally, no clinical or environmental relevant shedding or spreading to the environment is foreseen. The VSV-GP128 candidate viral therapeutic vaccine was shown to be genetically stable and there is no environmental risk of reversion to virulence through recombination or reassortment.

B. **Information relating to the recipient or parental organism from which the GMO is derived**

1. Recipient or parental organism characterisation:

The parent virus VSV-GP is a genetically engineered virus which does not carry the multi-antigenic domain and does not exist in nature.

Indicate whether the recipient or parental organism is a:
(select one only)

viroid	(.)
RNA virus	(X)
DNA virus	(.)
bacterium	(.)
fungus	(.)
animal	
- mammals	(.)
- insect	(.)
- fish	(.)
- other animal	(.)
(specify phylum, class)	…
other, specify	…

2. Name

(i)	order and/or higher taxon (for animals)	Rhabdoviridae family
(ii)	genus	Vesiculovirus
(iii)	species	Vesicular stomatitis virus
(iv)	subspecies	…
(v)	strain	Indiana
(vi)	pathovar (biotype, ecotype, race, etc.)	VSV
(vii)	common name	VSV-GP

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (X) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

Atlantic	..
Mediteranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesian	..

(ii) No (X)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (X)

Wt-VSV is reported to exist exclusively in the western hemisphere. It is maintained in stable ecologic niches in Central and South America and Mexico and emerges from tropical areas to cause sporadic epidemics in cooler climates during the summer months.

4. Natural habitat of the organism

(a) If the organism is a microorganism

water	(.)
soil, free-living	(.)
soil in association with plant-root systems	(.)
in association with plant leaf/stem systems	(.)
other, specify …	(X)

VSV-GP is not found in a natural habitat.

(b) If the organism is an animal: natural habitat or usual agroecosystem:

Not applicable

5. (a) Detection techniques

RT-PCR

(b) Identification techniques

RT-PCR or Sequencing

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (X) No (-)
If yes, specify

VSV-GP is assigned to risk group 2 (BSL 2)

.7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (-) No () Not known (X)

If yes:
(a) to which of the following organisms:

humans	(-)
animals	(-)
plants	(.)
other	(.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

As VSV-GP is a genetically modified virus there is no natural host and no clinical data is currently available, but it was demonstrated that in contrast wt-VSV it is affecting life stock.

What is known from wt-VSV is that it is not considered a human pathogen, however, it was reported that humans living in enzootic areas have a high seroprevalence rate and that intimate contact with infected animals may lead to infection of humans with flu-like symptoms. It is believed that transmission to humans occurs through direct contact with active lesions or saliva containing infective wt-VSV. There are no reports of humans transmitting the infection to other humans or to animals, although transmission via contaminated equipment, hands, gloves, and clothing probably occurs. Veterinarians, animal health technicians, livestock handlers, laboratory personnel and others working closely with infected animals or live virus are at increased risk. Nevertheless, most seropositive people have not had clinical disease, or have had mild disease symptoms (usually a mild flu-like illness).

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

Not applicable.

(b) Generation time in the ecosystem where the release will take place:

Not applicable

(c) Way of reproduction: Sexual .. Asexual X..

Factors affecting reproduction:

Not applicable

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	…

(b) relevant factors affecting survivability:

VSV based viruses are inactivated by sunlight and does not remain viable for long periods in the environment except in cool, dark places. Common disinfections agents (alcohols, aldehydes, and detergents) appear to be highly efficient for virus inactivation, as well as the temperature higher than 55°C.

VSV is susceptible to all disinfectants for enveloped viruses and is inactivated by 1% cresylic acid, phenolics, chlorinated phenol, 2.5% phenol, 0.4% HCl, 2% sodium orthophenylphenate 14, and sodium hypochlorite. They are inactivated by heating (60°C, 30min), and can survive temporarily on contaminated surfaces.

10. (a) Ways of dissemination

VSV-GP is a recombinant virus and there is no natural way of dissemination other than direct contact.

(b) Factors affecting dissemination

Not known

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
…, B/../../…

C. Information relating to the genetic modification

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
Compared to the parent virus VSV-GP, VSV-GP128 carries a gene coding for a multi-antigenic domain comprising of colorectal cancer specific antigens i.e. carcinoma embryonic antigen (CEA), survivin and achaete-scute complex homolog 2 (ASCL2), integrated in its linear, negative-sense, single-stranded RNA genome.

The Mad is included to induce an immune response against the included tumour antigens.

3. (a) Has a vector been used in the process of modification?
Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Yes (-) No (X)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(.)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify	…

(b) Identity of the vector

(c) Host range of the vector

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype

Yes (.) No (.)

antibiotic resistance	(.)
other, specify	…

Indication of which antibiotic resistance gene is inserted

(e) Constituent fragments of the vector

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	…

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify	plasmid-based virus rescue system

6. Composition of the insert

(a) Composition of the insert

The Mad is composed of three tumor specific antigens, i.e. carcinoma embryonic antigen (CEA), survivin and achaete-scute complex homolog 2 (ASCL2), integrated in a linear, negative-sense, single-stranded (ss) RNA genome.
The VSV-GP128 clinical vector includes the sequence of the Mad antigens which was inserted into the pVSV-LCMV-GP (WE-HPI) in between the GP coding sequence and the L coding sequence.

(b) Source of each constituent part of the insert

See under 6 (a)

(c) Intended function of each constituent part of the insert in the GMO

The Mad is included to induce an immune response against the included tumor antigens.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify …

In VSV-GP128; the Mad sequence was inserted into the viral genome

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (-)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals ()
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) …

other, specify:
The multi-antigenic domain (Mad) is coding for three tumor specific antigens: carcinoma embryonic antigen (CEA), survivin and achaete-scute complex homolog 2 (ASCL2), all derived from human genes.

2. Complete name

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	
(iv)	species	
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(viii)	common name	

Not applicable

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

If yes, specify the following:

(a) to which of the following organisms:

humans	()
animals	(.)
plants	(.)
other	…

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
Yes (.) No (X)
If yes, specify

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (X) Not known (.).

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?
Yes (.) No (X) Not known (.)
Specify The Mad antigen does not impact virus properties

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (.) No (X) Unknown (.)
Specify The Mad antigen does not impact virus properties

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (.) No (X) Not known (.)
Specify The Mad antigen does not impact virus properties

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?
Yes (.) No (X) Not known (.)
Specify The Mad antigen does not impact virus properties

2. Genetic stability of the genetically modified organism

Genetically stable

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
Yes (.) No (-) Unknown (X)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)
…

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

RT-PCR

(b) Techniques used to identify the GMO

RT-PCR or Sequencing

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The purpose of the release of VSV-GP128 in the clinical trial is to evaluate its safety, tolerability, and anti-tumor activity together with other compounds already employed (ATP128 and BI 754091), in patients with stage IV colorectal cancer.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes () No (-)

If yes, specify

Not applicable.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

UZ Leuven
Herestraat 49, 3000 Leuven

UZ Antwerpen
UZA, Wilrijkstraat 10, 2650 Edegem

(b) Size of the site (m^2): … m^2
(i) actual release site (m^2): … m^2
(ii) wider release site (m^2): … m^2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

Not applicable as administration will only occur in the clinical sites.

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO

Not applicable. Administration will only occur in the clinical sites. With the procedures implemented to reduce spread of VSV-GP128 to the environment, it is highly unlikely that any animals will come into direct contact with the virus. Data from animal studies has indicated that viral shedding poses a negligible risk. However, patients are still given extensive biosafety advice before being discharged from the clinical facility, to further decrease the possibility of the GMO spreading to other species.

4. Method and amount of release

(a) Quantities of GMOs to be released:

Patients will be given one single intravenous dose of 10^7 $TCID_{50}$ VSV-GP128 while in the clinical setting.

(b) Duration of the operation:

Duration of the clinical trial (Q1 2022 -Q3 2023)

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of release

Appropriate risk management strategies are in place to avoid and/or minimise the risks of VSV-GP128 spread beyond the clinical site including.

- Design of the viral construct
- Control of virus spread of unintended release
- Transportation precautions
- Administration precautions
- Cleaning and waste management

The following instructions will be given to the patients to prevent dissemination. They are to be implemented for 7 days following VSV-GP128 administration, unless otherwise instructed:

- Avoid close contact with young children, pregnant women, immunocompromised people and livestock (e.g. pigs, cows, horses, etc.). When unavoidable, a surgical grade mask should be worn when within touching distance.
- Wash frequently your hands with soap and water or use alcohol-based products.
- Cover mouth and nose while coughing or sneezing with a single-use tissue and dispose dirty tissues after use.
- Ensure the surface injection site is covered with an airtight and watertight dressing for 2 days following VSV-GP128 treatment and avoid scratching the injection site.
- Ensure gloves are worn when changing dressing to ensure patient and close contacts do not come in contact directly with any of the dressings or with the injection site.
- Collect any trial waste (e.g. bandages, plasters), store separately and bring back to the clinical site, at your next visit, to be destroyed following the clinical site infectious waste protocol management.
- Avoid common usage of unwashed cutlery, crockery, and drinking vessels.
- Avoid common usage of injection needles, razorblades, toothbrushes and bath towels.
- In case of bleeding, disinfect and cover the wound with a plaster.
- Store any soiled clothing separately from any other people living in the same accommodation. Wash any clothes, household linens, cleaning cloths etc. either at 60°C (140°F) or using a washing detergent on a regular basis.

- Where possible use a separate toilet, adding bleach or equivalent products to the toilet after each use (including menstruation bleeding). Put all sanitary protections in a container (e.g. plastic bag) and return it to the clinic at your next visit.
- Avoid unprotected sexual intercourse.

5. Short description of average environmental conditions (weather, temperature, etc.)

Not applicable (the risk of release is unrelated to the Belgian climate which is temperate).

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.

Not applicable.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

(i)	order and/or higher taxon (for animals)	
(ii)	family name for plants	…
(iii)	genus	
(iv)	species	
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

Not applicable.

3. Any other potentially significant interactions with other organisms in the environment

Not applicable.

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

Yes (.) No (X) Not known (.)

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

Unknown.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

None

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:

VSV-GP128 is a single-stranded RNA virus, which does not use DNA to replicate. It also replicates in the cytoplasm, which means it does not come into close contact with the human host DNA, and so the risk of genes being transferred from the virus to humans is considered negligible.

(b) from other organisms to the GMO:

Not applicable.

(c) likely consequences of gene transfer:

Not applicable.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):

Not applicable.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

Not applicable.

H. Information relating to monitoring

1. Methods for monitoring the GMOs

Viral shedding will be closely monitored in the first VSV-GP128 cohort. Other methods to monitor the effects of VSV-GP128 include both safety and efficacy assessments.

2. Methods for monitoring ecosystem effects

No ecosystem effects are expected because shedding is expected to be negligible and shedding will be confirmed in the clinical trial.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Not applicable

4. Size of the monitoring area (m^2)
… m^2

Not applicable

5. Duration of the monitoring

Viral shedding will be monitored in the first VSV-GP128 cohort until at least three consecutive negative results are obtained.

6. Frequency of the monitoring.

The patient in the first VSV-GP128 cohort will be monitored for viral shedding on the day of treatment and repeated follow-up visits (refer to H5).

I. Information on post-release and waste treatment

1. Post-release treatment of the site

Disposal of Patient Samples must be carried out in accordance with the rules related to the management of medical wastes that are specified by Clinical sites.

All patient materials should be handled as infected articles. For disposal, all materials should be decontaminated by steam sterilization, chemical disinfection, and/or incineration; needles and sharp instruments should be stored in dedicated containers. Note: Recommendations should also be adapted following local protocols and regulations.

2. Post-release treatment of the GMOs

(a) Type and amount of waste generated

Empty vials and used vials and the used delivery system components (e.g. needles, catheter, syringes), gauzes and personal protective equipment and components used for collecting body fluids samples after administration.

(b) Treatment of waste

Disposal of VSV-GP128 must be carried out in accordance procedures in use at the clinical sites. Disposal of devices and equipment which comes into contact with VSV-GP128 should be disposed of according to local law.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

In case of self-accidental injection of medical personnel, the injection site will be disinfected, and personnel will be followed up according to site procedures.

2. Methods for removal of the GMO(s) of the areas potentially affected

After patient's discharge, potentially contaminated surfaces (e.g. bathroom equipment: faucet, toilet, sink, etc.), room furniture (nightstand, table, chair, floor, hand rails etc.) should be disinfected following applicable local cleaning procedures.

Any spills or soiled material handled per standard procedures for infectious/contaminated material.

Inactivation: VSV-GP128 is susceptible to all disinfectants for enveloped viruses and is inactivated by 1% cresylic acid, phenolics, chlorinated phenol, 2.5% phenol, 0.4% HCl, 2% sodium orthophenylphenate 14, and sodium hypochlorite. Physical inactivation: VSV-GP128 is inactivated by heating (60°C, 30min). VSV-GP128 survives temporarily on contaminated surfaces.

Handling of spills: Inform and warn colleagues in direct proximity. Allow aerosols to settle and, wearing protective clothing, gently cover spill with paper towels and apply appropriate disinfectant, starting at the perimeter and working towards the center. Allow sufficient contact time before cleaning up (30 min).

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

Not applicable.

4. Plans for protecting human health and the environment in the event of an undesirable effect

Even though the release of the GMO from patients to a third party is highly unlikely, in case flu-like symptoms occur these will be symptomatically treated.