Oragenics, Inc.
4902 Eisenhower Blvd., Suite 125
Tampa, FL 33634 United States

GMO Deliberate Release Notification

INFORMATION FOR THE PUBLIC[1]

A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF TOPICALLY-APPLIED AG013 FOR THE ATTENUATION OF ORAL MUCOSITIS IN SUBJECTS WITH CANCERS OF THE HEAD AND NECK RECEIVING CONCOMITANT CHEMORADIATION THERAPY

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Prepared by:	**Dr. Alan Joslyn, CEO Oragenics**

[1] *This document is in line with the "Guidelines To Compile The Public Dossier - Deliberate releases of genetically modified micro-organisms for experimental purposes (part B)" of the Biosafety Advisory Council (version of 26 February 2003). Mandatory text is presented in italics.*

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1. REGULATORY FRAMEWORK AND AUTHORIZATION PROCEDURE

The release of genetically modified organisms (GMOs) in the environment is strictly regulated at European level by directive 2001/18/EC of 12 March 2001 repealing directive 90/220/EEC and at Belgian level by the Royal Decree of 21 February 2005 regulating the deliberate release and/or marketing of GMOs or products that contain GMOs into the environment repealing the Royal Decree of 18 December 1998.

To ensure the safe use of GMOs, the provisions of the Royal Decree above stipulate that the release of GMOs for experimental aims is prohibited without prior consent from the competent Minister. The decision is based on a thorough evaluation of the biosafety of the planned release, which is conducted by the Biosafety Advisory Council, composed of different Scientific Committees grouping independent experts from Belgian universities and governmental institutes.

To acquire the necessary authorization from the competent Minister, the company Oragenics, Inc. submitted an application dossier to the competent authority. On the basis of the advice of the Biosafety Council, the competent minister could grant permission to the company Oragenics, Inc. to conduct experiments with transgenic Lactococcus lactis as stipulated in the application ***B/BE/x.***

The release will take place at locations in Flanders/Wallonia/Brussels as a consequence of clinical trials conducted at the sites listed below. It is expected to start in July 2018 and to be completed by June 2019 (Last Patient Completes Treatment) and by July 2020 (Last Patient Completes Long-term Follow-up, equals last patient last visit).

- *UZ Leuven, 3000 Leuven*
- *Grand Hôpital de Charleroi, Site Notre Dame, 6000 Charleroi*
- *Institut Jules Bordet, 1000 Brussels*
- *UZ Antwerpen, 2650 Edegem*
- *UZ Brussel, 1090 Brussel*
- *AZ Sint-Maarten, Campus Rooienberg, 2570 Duffel*

2. DESCRIPTION OF THE GENETICALLY MODIFIED MICRO-ORGANISM (GMM):

AG013 is the mouth rinse formulation of genetically modified (GM) *L. lactis* strain sAGX0085, engineered to secrete human Trefoil Factor 1 (hTFF1).

L. lactis that is not modified (*L. Lactis* strain MG1363) is commonly used to produce dairy products including buttermilk and cheeses. To make AG013, the DNA of *L. lactis* has been changed in the laboratory to secrete (release) a protein called human Trefoil Factor 1 (hTFF1). hTFF1 is normally secreted in saliva and intestines. Trefoil factor has been shown to be important in protecting and healing mucosal tissues, such as the tissue in the mouth, when these tissues are damaged by cancer therapies such as concomitant chemoradiation therapy.

The proposed indication of AG013 is to reduce the signs and the symptoms of the side effect oral mucositis (OM) related to radiotherapy (RT) and/or chemotherapy (CT). Subjects with OM get soreness,

irritation, and ulcers in the mouth and may have a hard time eating, drinking or swallowing as a result of their cancer treatment.
L. lactis is one of the most important microorganisms involved in the dairy industry. *L. lactis* was originally isolated from raw milk and this is one of the few environments where it can survive. *L. lactis* can also be found in man and in animals, soil, effluent water and plants, but these environments do not necessarily sustain growth. *L. lactis* is non-disease causing (non-pathogenic) and does not build survival structures such as spores. The presence of the *htff1* gene does not change that.

L. lactis strain MG1363 can no longer grow in milk or in any other natural environment. The genes to use the necessary nutrients of milk are removed. As a consequence, MG1363 can only grow in artificially supplemented culture conditions. The previous trial has shown that this drug product is safe and does not survive outside the human body.

The genetically modified *L. lactis* strain MG1363 is even more restricted: the bacterium contains the gene for hTFF1, stably inserted in the chromosome where it replaces a gene needed for thymidine (a building block of DNA) production. This makes the recombinant strain dependent on addition of thymidine to the culture. Without thymidine, the bacterium cannot survive.

The gene construct also contains a signal to excrete the hTFF1 protein outside the bacterium. The bacteria will produce and excrete hTFF1 in the mouth to the benefit of the patient.

The clinical formulation of AG013 is an oral, topical administration in the form of a mouth rinse. Therefore, after administration the bacteria end up in the sewage system, directly or, in case of accidental swallowing by the patient, via the faeces. Only a limited number of bacteria survives the passage through the body. Bacteria will degrade soon afterwards.

3. TYPE AND PURPOSE OF THE ENVISAGED TRIAL:

AG013 was evaluated for the first time in humans in a Phase 1b clinical trial in the United States of America. This study demonstrated that AG013 was generally safe and well tolerated by head and neck cancer patients who were eligible for induction chemotherapy prior to undergoing radiotherapy. The study also showed initial efficacy. AG013 has also been studied in healthy volunteers in Belgium.

The proposed phase 2 trial is the next step in the global clinical development program of AG013 after the first two studies.

This Phase 2 trial titled “Multi-center, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Topically-applied AG013 for the Attenuation of Oral Mucositis in Subjects With Cancers of the Head and Neck Receiving Concomitant Chemoradiation Therapy”, will be conducted in the United States and Europe at multiple clinical sites. In total, approximately 200 subjects will be recruited.

During the study, eligible subjects will use the mouth rinse (containing AG013 or placebo) three times per day from the first day of radiotherapy until two weeks following the last day of radiotherapy. Subjects will rinse with the suspension for 30 seconds three times each day using the assigned IMP. The suspension should then be expectorated into a sink or toilet. The active treatment phase lasts for 7 to 9 weeks, depending on the duration of radiotherapy.

The efficacy and safety of AG013 will be compared to a placebo. After screening, subjects will be randomized to either an AG013 treatment arm or a placebo arm according to a 1:1 randomization ratio. In Belgium 6 hospitals take part in the study. About 15 subjects will be recruited per treatment group. This means that a total of 30 subjects is envisaged in Belgium.

The subjects are selected according to very stringent criteria. This is why a multi-centre approach, spanning several countries, is required. The studies are so-called ambulatory/outpatient studies *i.e.* the subjects do not reside in the clinical trial centre during the trial. They only visit the centre for their chemoradiation therapy and at regular times the patient will return to the clinical trial centre for a study visit as specified in the study protocol. The subjects receive a weekly treatment package at each weekly visit.

4. RESEARCH AND DEVELOPMENT FRAMEWORK:

Oral mucositis is a painful, common toxicity of many forms of chemotherapeutic drugs and radiation therapy used for the treatment of cancer. Clinically, oral mucositis results in a range of mucosal damage that extends from burning erythema to opioid-requiring, full-thickness mucosal ulceration.

Oral mucositis is among the most frequently reported adverse events associated with cancer treatment leading to increased use of painkillers and antibiotics, febrile days, need for parenteral nutrition, length of hospital stay, unplanned and emergency room visits, and total charges, all of which have a negative impact on health and economic outcomes. Oral mucositis is a severe complication of treatments of patients with head and neck cancer.

Small proteins from the Trefoil Factor (TFF) family are made by the human body for the protection of the gastrointestinal tract against mucosal damage and play an important role in its subsequent repair. Oral TFFs form a mucus layer over the epithelia of the mouth, acting as a physical barrier against bacteria and noxious environmental agents. Moreover, they have wound-healing properties and are important in protecting and healing mucosal tissues.

The available data suggest that TFFs may provide a novel pharmacological tool for the prevention and treatment of human gastrointestinal diseases. Importantly, research has shown that topical oral application of recombinant *L. lactis* strains engineered to secrete either hTFF1 or hTFF3 significantly reduced the severity and course of radiation-induced oral mucositis in an established hamster model.

AG013 has been evaluated in many animal studies in which it showed to be safe and in which it reduced oral mucositis.

To date, AG013 has been studied in humans in 2 studies: a Phase 1b clinical study and a Phase 1 study in healthy volunteers.

The Phase 1b study, the first in humans, achieved its primary objective by demonstrating that AG013 was generally safe and well tolerated. The exploratory efficacy results showed that subjects who received AG013 had a lower percentage of days with ulcerative mucositis, and more subjects who received AG013 on any dosing schedule had no or only 1 day of ulcerative mucositis compared to subjects who

received placebo. In addition, subjects who received AG013 had fewer unplanned office and emergency room visits compared to subjects who received placebo.

The Phase 1 clinical trial in healthy volunteers in Belgium was the second clinical trial of AG013. The aim was to determine the pharmacokinetic profile of AG013 and to study the influence of food and beverage on the activity of AG013. This study demonstrated that live AG013 bacteria adhere to the oral mucosa and actively secrete hTFF1. In addition, results show that AG013 must be dosed after meal intake to ensure optimal exposure.

The planned Phase 2 clinical trial is a continuation of this development. Based on the results of the earlier Phase 1b trial, this plan includes the same *L. lactis* strain at one of the dosing frequencies assessed during the Phase 1b trial: three mouth rinses per day ($2x10^{11}$ CFU/mouth rinse).

Oragenics' overall objective of the development program is to establish AG013 as a therapeutic option, and gain marketing approval for reduction of the signs and the symptoms of radiation therapy and/or chemotherapy induced oral mucositis.

5. POTENTIAL BENEFITS OF THE PLANNED RELEASE:

The planned release is a further step in the development of a new strategy to alleviate oral mucositis. Despite recent advances, and although oral mucositis is frequently reported in cancer patients, treatment options are very sparse. Thus, for the majority of subjects receiving cytotoxic chemotherapy and/or head and neck radiation therapy, oral mucositis represents an important, unmet clinical need.

6. ASSESSMENT FOR POTENTIAL RISKS FOR THE HUMAN HEALTH AND ENVIRONMENT:

L. lactis is commonly found in and added to food products. *L. lactis* is one of the most important microorganisms involved in the dairy industry. The majority of the industrially produced bacteria do not survive outside the dairy environment. It is not classified as a hazardous organism. It does not produce survival structures such as spores.

L. lactis can be found in a whole range of environments, but these are not necessarily ecological niches. In spite of the wide spread use and massive discharge in the environment it has not been identified as invasive or disruptive. Growth can only be sustained in a selected number of nutritionally favourable areas such as milk. *L. lactis* does not multiply in or colonize humans or mammals.

L. lactis strain MG1363 only grows in artificially supplemented culture conditions as the genes to use the necessary nutrients of milk are removed. MG1363 does not produce antibiotics, but is sensitive to a large range of them.

The hTFF1 producing strain, *L. lactis* strain sAGX0085, also lacks the ability to produce thymidine, without which it will die. It is highly unlikely that the genetically modified microorganism will reacquire the ability to produce thymidine. Also, it is unable to transfer the genetic modification to other microorganisms. No specific interactions with non-target organisms have been identified.

In an ambulatory/outpatient study, the administration of the study drug may occur in the clinical trial centre or outside of the hospital (*i.e.* most likely at home). Subjects will rinse three times per day with AG013 mouth rinse, the active treatment phase will last for 7 to 9 weeks. Most of the bacteria will be spat out and released directly in the sewage system. However, some bacteria, once administered, will reside in the mouth for some time before following the faecal flow. AG013 is expected to be present in the oral cavity in saliva, up to 24 hours after dosing and was not detected in fecal samples. The administration, rinsing and excretion (via faeces) are not necessarily limited to the home of the patient. In consequence, the national territory is considered as the wider potential release area. It can be expected that a few days after the last treatment, the shedding of live bacteria stops.

Accidental spillage: sAGX0085 could leak into the environment due to accidental spillage during reconstitution or during administration, or due to rupture of the pre-packed product. sAGX0085 cannot survive outside of artificially-supplemented laboratory conditions and will be rapidly eliminated. The quantity of such spillage will normally be limited to one treatment dose, but the environmental containment system is robust and its efficiency will not be influenced by the quantity of spillage that might occur (e.g. a large spillage consisting of a complete one-week treatment package). The affected area can be decontaminated with a standard detergent (soap) or bleach. Detailed instructions on the actions to be taken in case of spillage or accident are presented in a Question & Answer document, which will be provided and explained to the subject. There is little possibility that sAGX0085 could spread to other persons or to the environment due the environmental containment strategy.

It cannot be excluded that valuable biotopes, protected areas or drinking water supplies will be exposed. However, exposure to *L. lactis* already occurs. The modified strain has no additional features that make exposure more likely. On the contrary, as it is totally dependent on the presence of thymidine to survive, any exposure will be even more limited in time. Whereas the release in the environment can be concluded to be similar to that normally encountered for *L. lactis*, the modifications characterizing the GMO ensure that the strain cannot survive in this habitat anymore.

Trefoil factors are present in mammals, birds and amphibians to protect the mucosa in the gastrointestinal tract. Preclinical toxicity studies with the human TFF1 expressing *L. lactis* on rats and dogs did not result in any adverse effect. No effect at all is expected on plants.

The *htff1* gene in the GMO is a unique, synthetic gene which can be distinguished from the native *htff1* gene. It can be detected via a technique called polymerase chain reaction (PCR).

This notification concerns a deliberate release of GMO for experimental purposes. Therefore, as a general rule the use of this material for any other purpose is prohibited. There is little possibility that sAGX0085 could spread to other persons or to the environment due the environmental containment strategy.

7. CONTAINMENT AND CONTROL

In the clinical trials, the drug product (containing the bacteria) is available as a powder, to be reconstituted in a liquid. In the event that the packaging is disrupted, the powder quickly degrades after being in contact with moisture and warmth. The microorganism is sensitive to temperatures above 40°C, low pH, air drying, direct sunlight, UV, soap, bleaching agents, antibiotics and high salt concentration

solutions. The quantity of a spillage will be limited (one dose). The affected area can be decontaminated with a standard detergent (soap) or bleach.

Brief contact with the powder and the solution is possible at time of reconstitution of the mouth rinse and when administered. The participant only receives the necessary material for a one week treatment period. At the same time, instructions are provided and explained in order to ensure compliance to treatment. Other family members may be exposed when handling empty bottles and possibly material with shed bacteria. Standard hygienic practices should be sufficient to limit or prevent significant exposure.

Once administered and after residing in the mouth for some time, the bacteria will follow the faecal flow. The administration, rinsing and excretion (via faeces) are not necessarily limited to the home of the patient. In consequence, the national territory is considered as the wider potential release area. In the Phase 1b healthy volunteer study, no live bacteria were recovered in faeces after a single dose. No specific treatment of the shedding environment is foreseen, as justified by the biological containment and the absence of any relevant impact on the environment. Also, the public at large usually has no access to the sewage system. If required, a standard antibiotic treatment would suffice to inactivate the bacteria.

At regular intervals, the subjects will return to the hospital not only for examination but also to return used and unused study drug packaging. The pharmacy of the hospital will destroy the material according to their institutional standards. At the clinical trial centre, standard precautions are in place. Investigators and other clinical staff can only be exposed during the handling of a treated subject or of specific material that has been in contact with the GM strain. Normal hygiene conditions for clinical staff should be sufficient. These include wearing disposable gloves and using disposable wipes when handling any materials that came in contact with the GM strain. All waste materials will be collected and handled as medical waste.

Transmission through air is not an issue. Aerosol formation of liquids that could contain GM bacteria can be excluded. Only the removal of blood samples requires the use of syringes. As sAGX0085 has never been detected in blood samples during non-clinical and clinical studies, syringes can be handled following standard clinical procedures.

In all of these cases, survival of the bacteria will be extremely limited in time, and during this potential survival period the very limited amount of bacteria potentially present will not be metabolically active.

8. RESPONSIBILITIES OF THE NOTIFIER:

The consent that could be given to the notifier by the competent Minister stipulates that the notifier takes complete civilian liability regarding the damage that could be caused by the deliberate release to the health of humans, animals, or environment.

9. INSPECTION BY THE PUBLIC AUTHORITIES:

Inspectors are in charge of inspecting the trials for compliance with the conditions specified in the consent and to investigate potential breaches of the consent. In case where mismanagement or fraud is identified specific sanctions will be imposed.

10. ACTIVITY REPORT:

At the end of the trial an activity report prepared by the notifier needs to be delivered to the competent authority. This activity report includes at least the following data:

- *the site and period of release,*
- *the precise nature of the actually released GMMs,*
- *the aim(s) of the trial,*
- *the measures that were taken to prevent unwanted release of transgenic material,*
- *if applicable, the measures that were taken to protect the subject (patient/animal) during administration of the GMM-containing study drug,*
- *if applicable, the measures that were taken to protect the relatives of the treated subjects,*
- *the measures that were taken to protect the workers who had to manipulate the GMM-containing material,*
- *the method used for the destruction of the unused or contaminated material,*
- *the results obtained during the trial,*
- *an overview of the monitoring of patient/animal for GMM shedding,*
- *an overview of the monitoring of GMM or recombinant DNA in the environment.*

11. CONTACT:

If you have any comment on the public dossier or our activities or wish to obtain additional information on the deliberate release, please contact us at the following address.

Notifier:
Name of company: Oragenis, Inc.
Address: 4902 Eisenhower Blvd., Suite 125, Tampa, FL 33634 United States
Telephone: +1 813-286-7900
Fax: +1 813-286-7904
Email: info@oragenics.com
Web site: www.oragenics.com

Contact person:
Name of contact person: Dr. Alan Joslyn, CEO
Address: 4902 Eisenhower Blvd., Suite 125, Tampa, FL 33634 United States
Telephone: +1 813-286-7900
Fax: +1 813-286-7904
Email: ajoslyn@oragenics.com

You can also have access to a summary of the notification (SNIF) on the web site of the Joint Research Centre of the European Commission (http://gmoinfo.jrc.it/). Comments can be addressed to the Commission via this web site.