

SOBERANA, Cuba's COVID-19 Vaccine Candidates: Dagmar García-Rivera PhD Director of Research, Finlay Vaccine Institute

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On August 13, 2020, Cuba's national regulatory agency, the Center for Quality Control of Medicines, Equipment and Medical Devices (CECMED), authorized clinical trials for SOBERANA 01—Cuba's first vaccine candidate and the first from Latin America and the Caribbean. On August 24, parallel Phase I/II double blind, randomized, controlled clinical trials were launched at clinical sites in Havana to evaluate the vaccine's safety and immunogenicity. Analysis of results and development of different formulations are currently under way and Phase III clinical trials are planned for early 2021. At the time of writing, a second vaccine candidate, SOBERANA 02, was in late-stage development and preparing to begin separate trials this fall.

Cuba's biotech industry, comprised of more than 30 research institutes and manufacturing companies in the state-owned conglomerate BioCubaFarma, has developed and distributed vaccines according to international standards of good clinical and manufacturing practices and protocols for decades. BioCubaFarma supplies over 800 products to Cuba's national health system—349 of those are on Cuba's Basic Drug List, the medicines approved for use in the country's health system. Additionally, BioCubaFarma has 2438 patents registered outside Cuba and its products, including vaccines, medicines and medical equipment, are in 100 simultaneous trials at 200 clinical sites and are registered and sold in more than 50 countries.

These factors proved advantageous for making a fast, confident pivot towards COVID-19 vaccine development. Specifically, these antecedents meant all necessary technical capacities and regulatory certifications were already in place. Founded in 1989, CECMED was certified as a WHO Level 4 Regulatory Authority of Reference for vaccine control (the highest certification level conferred) in 2017; also in 1989, a team at Cuba's Finlay Vaccine Institute led by Dr Concepción Campa, developed VA-MENGOC-BC, the world's first safe, effective vaccine against serogroup B meningococcus; and in 2000, Cuba's recombinant hepatitis B vaccine received WHO-PAHO pre-qualification. To date, millions of people in Cuba and elsewhere have been immunized against a variety of diseases with vaccines from the island.

Shortly after COVID-19 was declared a pandemic by WHO, this expertise was marshaled to develop a Cuban vaccine



against the disease. Researchers from the Finlay Vaccine Institute (IFV), the Molecular Immunology Center (CIM) and the University of Havana's Chemical and Biomolecular Synthesis Laboratory, with support from other BioCubaFarma enterprises, are leading the project aimed at delivering a safe, effective vaccine in 2021.

The SOBERANA team, which is working on two vaccine candidates, SOBERANA 01 and SOBERANA 02 and several formulations thereof, is led by Dr Vicente Vérez-Bencomo, IFV Director, Dr Yury Valdés Balbín, IFV Deputy Director; and Dr Dagmar García Rivera, IFV's Director of Research, a post she has held since 2014. A vaccine expert with a PhD in pharmaceutical sciences, Dr García Rivera is recognized for her multiple contributions to Cuban science, including development of a pneumococcal conjugate vaccine that is concluding Phase III clinical trials in preparation for introduction into the country's national health system. She was awarded Cuba's Annual Health Prize, the national prize of the Cuban Academy of Sciences on three occasions, and in 2019, received the Carlos J Finlay Order of Merit. Dr Garcia Rivera has represented Cuba in meetings of WHO, UNICEF and other multilateral organizations. In late September, with safety and immunogenicity trials for SOBERANA 01 continuing apace, Dr Garcia Rivera paused her feverish work schedule for this exclusive interview with *MEDICC Review*.

MEDICC Review: Cuba's first vaccine candidate, SOBERANA 01, qualified for clinical trials rapidly—in just 90 days. Can you describe the research process?

Dagmar García: In January 2020, Cuba drafted its National COVID-19 Prevention & Control Plan and convened an innovation committee to work on a vaccine. But since we're dealing with a novel coronavirus, there wasn't enough scientific evidence available at that time for us to determine what kind of candidate might be appropriate.

So our first challenge as researchers was to amass all the scientific evidence and analyze it. And analyze it again. And then re-analyze it, incorporating new studies and scientific information as it emerged. We had to understand the physiopathological mechanisms of the virus, as well as the nature of the protective immune response the virus induced in infected people.

We have a situation with the emergence of SARS-CoV-2 whereby the virus and its devastating consequences advanced faster than our knowledge base. Research conducted globally becomes enormously important in this context.

MEDICC Review: And Cuban researchers had access to this research?

Dagmar García: Scientific research and publishing took an unprecedented turn with COVID-19: journals worldwide provided open access to their publications, guaranteeing broad, timely access to the information needed to help control the epidemic. This allowed us to incorporate new knowledge about the virus, the disease and the relevance of potential antigens for vaccine candidates on a daily basis.

I think this open-access model for knowledge-sharing should become the norm. And we hope it does—access to scientific knowledge should not be limited.

Access to scientific knowledge should not be limited

MEDICC Review: Unprecedented also, is the adjustment of regulatory mechanisms to develop a vaccine as fast as possible. What implications does this have—for the vaccine itself and related bioethics protocols?

Dagmar García: We're in the midst of a global health emergency. Normally it takes an average of 10 years to develop a vaccine, but we don't have that luxury with COVID-19. So regulatory mechanisms have been reorganized to shorten the development cycle to produce a vaccine as quickly as possible. In fact, most national regulatory authorities (NRAs) in those countries with vaccine candidates in development or clinical trials have made their regulatory mechanisms more flexible, permitting overlap of different phases. But that does not mean violating the ethical research principles or the necessary steps to develop and register a vaccine once it has proven safe and effective.

Our clinical trials are designed and conducted according to the highest international standards and established best practices; a vaccine's target population is a healthy population, which explains why the vaccine industry is the world's most highly regulated. Transparency is mandatory. Cuba practices

transparency and has shared all the necessary information throughout this vaccine development process. All our clinical trial protocols are published in the Cuban Public Registry of Clinical Trials (a WHO-accredited primary registry since 2011 and member of WHO International Clinical Trials Registry Platform, ICTRP; <https://rpcec.sld.cu>, Eds), a step required of all trials globally. And our national media regularly report to a broader public on the progress of SOBERANA 01.

Both our vaccine candidates, SOBERANA 01 and 02 have applied for patent registration with the Cuban Office of Industrial Property and our scientific results will be submitted to peer-reviewed journals once they're ready.

Cuba's biotechnology sector has been awarded 10 gold medals from the World Intellectual Property Organization (WIPO), including for the VA-MENGOC-BC vaccine developed by the Finlay Vaccine Institute (1989) and for Quimi-Hib developed by the University of Havana's Chemical and Biomolecular Synthesis Laboratory (2005).

MEDICC Review: Globally, over 40 vaccines have reached the stage of clinical trials in humans, using different technologies. What type of vaccine is SOBERANA 01?

Dagmar García: By March 2020, we began to see vaccine candidates that employed more traditional technologies—like those using inactive viruses to provoke a protective immune response. Given the urgency for a potential vaccine, certain processes were sped up allowing vaccine prototypes using newer technologies still in development to proceed to clinical phases. Adenoviral vector vaccine candidates and those using messenger RNA (mRNA) technology, for example, are among those not yet proven effective in humans.

But given our past experience, knowledge and success with other vaccines, we leaned towards a protein-subunit vaccine. The subunit vaccine platform is well established in Cuba. Importantly, VA-MENGOC-BC, IFV's meningitis B vaccine, is a subunits vaccine developed over 30 years ago and is a key component in our SOBERANA vaccine candidates. We have other subunit vaccines in our portfolio, including a recombinant hepatitis B vaccine and the *Haemophilus influenzae* type b (Hib) vaccine using a synthetic antigen, the first of its kind in the world (Hib vaccine development was headed by Dr Vicente Vérez-Bencomo; for more on his work and this vaccine, see *MEDICC Review* October 2007, Vol 9, No 1, Eds). The pentavalent vaccine used to vaccinate all Cuban children under one year old has subunit components (introduced in 2006, this Cuban-manufactured vaccine immunizes children against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b, Eds).

MEDICC Review: Can you explain how the Cuban COVID-19 subunit vaccine candidate works and if it has inherent advantages?

Dagmar García: For this type of vaccine to be effective, its crucial to know which part of the virus subunit, which antigen, is most significant. This took us more time to figure out. But once it became clear that the most relevant antigen is the receptor-



binding domain (RBD) of the viral Spike (S) glycoprotein—the protein that allows SARS-CoV-2 to invade human cells through the angiotensin-converting enzyme 2 or ACE2 receptor—this is where we focused our research. Using established genetic engineering methods and biotechnology processes, our colleagues at CIM successfully produced the RBD protein in mammalian cells. This gave us a well-defined and stable molecular structure with which to continue research.

Our first candidate, SOBERANA 01, is a two-dose vaccine based on an RBD amino-acid sequence that by design allows natural dimerization of two RBD molecules. This is combined with outer membrane vesicles of meningococcus B that act as an immunopotentiator. In short, the goal is to induce production of neutralizing antibodies against SARS-CoV-2.

“The presence of receptor-binding domain (RBD) antibodies 7 days post-vaccination in animals—and even more, after 28 days—is likely attributable to the immune-response strengthening ability of the outer membrane vesicles in which we formulated the vaccine.”

—Dr Dagmar García, *Mesa Redonda prime time TV news program, Aug 20, 2020*

There are several advantages to this approach. First, it uses an established technological platform proven over more than 30 years' experience—the platform used for our VA-MENGOC-BC vaccine. This translates into faster development and implies safety advantages for vaccine candidates. Second, we believe that a vaccine based on the RBD protein has high probabilities of success because immunological studies in patients recovering from COVID-19 show it's the most relevant viral component for inducing neutralizing antibodies.

Importantly, our biotechnology industry uses a model in which the scientific and technological capacities of each institution are coordinated, complementing one another. For example, for over 20 years, CIM has worked in large-scale production of complex recombinant proteins in mammalian cells and has mastered the

necessary immunological techniques used in earlier development of their therapeutic cancer vaccines. The University of Havana's Chemical and Biomolecular Synthesis Laboratory, meanwhile, contributes molecular-level research. We work as a consortium, an alliance that has allowed us to make rapid progress towards a vaccine; none of our institutions could have developed a vaccine candidate this fast alone.

Finally, we know there will be COVID-19 vaccines available around the world. But for a country like Cuba, it's prudent and strategic to develop and manufacture our own vaccine. So for us a major advantage of SOBERANA 01 is that it's Cuban.

MEDICC Review: Hence the name...

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Dagmar García: Calling our first vaccine candidate “SOVEREIGN 01” wasn't the original idea. This was simply the short name we gave to the clinical trial for this candidate. But once it was announced, the Cuban public reacted so enthusiastically that we decided to honor their support by grouping all our vaccine candidates under the name SOBERANA. The candidate now in Phase I/II trials is SOBERANA 01; our

second candidate—also based on the RBD protein but using a different platform—will begin trials soon, is SOBERANA 02, and so on. We hope both of these candidates, in one of their formulations, will demonstrate clinical efficacy.

MEDICC Review: What does the clinical trial process for SOBERANA 01 entail? How are trials conducted and by whom?

Dagmar García: The first step was receiving authorization for the trials from CECMED, Cuba's national regulatory agency. This requires submitting a dossier that contains detailed information related to the product's development and preclinical research: the chemical-pharmaceutical components, quality criteria, pharmacology and toxicology analyses in animal experiments, and protocols for clinical evaluation, among others. Once authorized, trial protocols and details must be published in the Cuban Public Registry of Clinical Trials. All clinical trials in Cuba require approval from the pertinent Independent Ethics Committee for Scientific Research before they can move forward—in this case, the National Toxicology Center (CENATOX).

The SOBERANA 01 clinical trials are administered by CENATOX. In 2009, this institute was certified according to best clinical practices by CECMED to conduct clinical trials, undergoes regular inspections by international agencies and has successfully conducted clinical trials with other biotechnology products. The design protocol calls for two doses, administered 28 days apart to healthy volunteers, including a randomized control group, which receives the VA-MENGOC-BC vaccine. It's hoped that the reactogenicity in both cohorts will be similar.

Inclusion criteria for the trial are strictly defined. Potential volunteers receive comprehensive information—written and ver-

bally—about what the trial entails and a description of how it will proceed so they can decide whether to participate. This includes the risks and benefits involved, the most common adverse events and what to do should such an event occur; we also explain to volunteers that conditions are guaranteed to treat adverse events and that they are free to leave the trial at any time.

Each person who decides to participate gives written informed consent. We then conduct comprehensive clinical studies, administer RT-PCR tests, and analyze other inclusion criteria like body mass index. Those testing positive for SARS-CoV-2 antibodies are not eligible to participate. Clinical evaluations occur 24, 48 and 72 hours after the first and second injections, followed by similar evaluations 14, 21 and 30 days after each injection. Followup with volunteers continues for two months and adheres strictly to the protocols established in our clinical trial design.

The trials are being conducted at certified clinical sites in Havana—we have extensive experience conducting trials with other vaccine candidates in other provinces, but due to epidemiological constraints and other logistical considerations, these phases are being conducted in the capital only. The 19–59 year old cohort received their first doses on August 24. Once preliminary safety of the vaccine was demonstrated with them, the second cohort, ages 60–80, received their first doses on September 11.

MEDICC Review: Inclusion criteria were for healthy adults from 19 to 80 years old, among others. Did you have challenges recruiting volunteers?

Dagmar García: The biggest challenge we faced recruiting volunteers is that we were inundated with requests. Too many people wanted to participate and we had to explain that this was a small-scale trial and that there would be more opportunities to volunteer in the future with this vaccine candidate or others. This includes the possibility of trials in other provinces, not just Havana. (Cuba's National Clinical Trials Site Network coordinates extension of trials to certified sites throughout the health system. For details see *The ABCs of Clinical Trials in Cuba*, MEDICC Review, July 2016, Vol 18, No 3, Eds).

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Courtesy IFV

This overwhelming response is partly due to the urgency for a COVID-19 vaccine, but also because there is public trust in these national programs, our vaccines and the science behind them. Cuba established its National Immunization Program in 1962 and has very high rates of coverage. This 'culture of health,' coupled with a transparent process, means trial volunteers are making quite a conscious decision to participate in trials.

MEDICC Review: Are there special considerations or precautions taken with the cohort of older adults—a vulnerable group, especially with regards to COVID-19—during the trials?

Dagmar García: The inclusion criteria and protocols for the older cohort are the same as those aged 19 to 59. However, to be eligible, those volunteers with chronic conditions had to demonstrate that they were clinically controlled. In addition to the periodic exams of every participant that I described, everyone also received a card that identifies them as a participant in the SOBERANA 01 clinical trial. And our entire health system is on alert. Should a volunteer become ill or have any health issue during the trial, including the two-month follow up period, they show this ID card to anyone at a health institution. This allows procedures to be implemented that are designed specifically for participants in this clinical trial. Furthermore, should a participant receive a positive RT-PCR test during the clinical trial, our national protocols for COVID-19 treatment are immediately activated and that person is removed from the trial.

MEDICC Review: Can you share initial results of the SOBERANA 01 trials?

Dagmar García: Our initial safety results are satisfactory, with no severe adverse events. For the next two months, we'll be gathering immunogenicity data to analyze which formulations, using different antigen levels, will proceed to future trials. Everyone is anxious for information and a successful vaccine, but at this point the clinical process is very slow and we can't speed it up. Two months are two months.

Looking forward, we have to demonstrate safety, immunogenicity and efficacy of whichever formulation of SOBERANA 01 (or another of our vaccine candidates) proceeds to the next phases of clinical trials. This is true for our vaccine candidates, as well as those in clinical trials around the world. Not enough time has elapsed to determine what level of immunity one of these candidates will confer or how long it will last—obviously this is incredibly important for any vaccine, including ours, and we will have to demonstrate this as well.

MEDICC Review: Will Phase III trials be conducted in Cuba?

Dagmar García: Phase III clinical trials involve thousands of people and while Cuba has a very willing population, anxious to

Phase II objective: Increased immune response (seroconversion of antibody titers equal to or greater than 4 times the initial baseline) in at least 50% of subjects compared to control group.

—Objectives and Variables, SOBERANA 01, Cuban Public Registry of Clinical Trials

Cuba's Women of Science

volunteer, we probably don't have the necessary COVID-19 incidence rate in our country to conduct trials of this scale.

While it is still too early to define where, when and how we would conduct these trials since this depends on the evolution of current clinical research, I can say unequivocally that if we need to go to another country to conduct Phase III trials, we will. Cuba has options for where that might be and all regulatory requirements of that country or those countries will be met to conduct those trials—with SOBERANA 01 or any other vaccine candidate.

MEDICC Review: One consideration around the world is production capacity for a COVID-19 vaccine. Assuming one of the SOBERANA candidates is approved for use, do you anticipate problems producing the doses needed?

Dagmar García: Our first challenge will be to produce enough doses of a safe, effective vaccine to satisfy domestic demand. Cuba is a small country of just over 11 million people, so we're not talking about huge demand, but this does mean producing several million doses so that we can vaccinate our entire population.

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and CIM are ready to start producing the number of doses needed for our population in existing, certified manufacturing plants conforming to international standards. Obviously, we will have to invest in upgrades and scale up production in some cases, but our capacity is already established and functioning.

Cuba also markets its biotech products, including vaccines, to dozens of countries. Once a SOBERANA vaccine becomes available for our population and then for sale abroad, these countries with which we already have contracts will logically be first in line.

MEDICC Review: What about the ingredients needed to produce the necessary doses? Does Cuba have them?

Dagmar García: We don't have in Cuba all the raw materials and supplies we'll need for the unprecedented scale of production that vaccinating our whole population requires. They have to be purchased and for this, we need financing. This is made infinitely more difficult by the US embargo—which as you know is an economic and financial embargo, hence we call it a blockade. It affects development of every economic and social sector in Cuba, including vaccines. Procuring the necessary reagents for

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research and the raw materials for production is a challenge we face daily due to limitations imposed by the embargo.

MEDICC Review: Once a Cuban vaccine is available, how will it be introduced into the health system? Will certain groups be prioritized?

Dagmar García: We'll be able to produce enough of the vaccine for our whole population. How will that be implemented and what groups will be prioritized? I can't give a precise answer because it's not an industry decision. But I can tell you that it will be a national strategy developed together with the Ministry of Public Health (MINSAP) based on the clinical data and number of doses available. Most likely, certain high-risk groups will be considered first....but that has yet to be decided.

MEDICC Review: The stress and urgency of your work, combined with the US sanctions and difficulties in Cuba, must be enormous. How do you and your team handle this?

Dagmar García: For months, we've faced the same problems created by the pandemic as everyone else in Cuba: the limitations, our kids at home instead of at school, our families in lockdown. We haven't rested since the vaccine development process started months ago. We've had no vacations. But we're deeply motivated by science: we maintain our spirits imagining months of hard work paying off with a successful vaccine. It's gratifying to imagine our work saving lives and benefiting our country.

I think this is the fundamental motivation for everyone working on our COVID-19 vaccine. You see it in people working overtime, making sure they make their deadlines, working weekends. But no one complains. Everyone is in good spirits and knows that results achieved today will be important for decisions taken tomorrow, so we just can't fall behind. The good will and optimism is real and runs deep.

A distinctive characteristic of Cuban science is that there are more women in the scientific sector than men and this is true for the SOBERANA 01 project as well. It helps that there are many young people on our team, too. This injects a vibrant spirit into our work.

Everyone is pulling together so that we can deliver a successful vaccine as soon as possible. Our families are a tremendous help in this regard: husbands, partners or other family members of many of the women working on SOBERANA, including mine, are at home as we speak taking care of the kids, cooking and cleaning. It would be very difficult for us to dedicate ourselves fully to this project otherwise.

MEDICC Review: Can you talk about the importance of international collaboration in confronting this pandemic? Will Cuba participate in the global COVAX initiative?

Dagmar García: This is the moment for international solidarity. No country can go it alone; a solution to this pandemic is only possible if it's contained the world over. I would add that the 'vaccine nationalism' we're seeing with COVID-19 is a direct result of globalization. Every time a new disease emerges, the gap between rich and poor countries is underscored. The difference with COVID-19, as opposed to Ebola for instance, is that this disease affects rich and poor countries alike—but access to an effective vaccine will not be equitable. In spite of WHO efforts, we are going to see differences in vaccine access on a global scale over the next year.

In terms of COVAX (COVID-19 Vaccines Global Access Facility), we're assessing the possibility of Cuban participation. We've been in talks with the Coalition for Epidemic Preparedness Innovations (CEPI, a co-leader with WHO and GAVI in the COVAX initiative to accelerate development, production and equitable access to a vaccine, Eds.), but we will have to wait for results.

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MEDICC Review: Looking ahead, what other Cuban research related to COVID-19 looks promising and what comes next for the SOBERANA project?

Dagmar García: Research is well under way by other Cuban scientists to determine whether genetics play a role in people's probability of developing severe cases of COVID-19 and if so, how. This research, led by the National Medical Genetics Center, includes people living with others infected by COVID-19 but who themselves have not become infected.

The National Blood Donors Group and the Hematology and Immunology Institute are co-leading a clinical research project involving use of blood plasma from patients recovering from COVID-19 used in therapies for those who have the disease. Of course, this research adheres to established clinical research protocols. This is just to mention a few of the projects under way for COVID-19 diagnosis and treatment.

As for our vaccine candidates, the balance of this year is dedicated to clinical trials of SOBERANA 01 and 02. Before the year is over, we will publish our pre-clinical trial results, and expect to publish the clinical trial results in early 2021. And while I can't pin down an exact date for when a vaccine will be ready, I can tell you two things: the first Cuban COVID-19 vaccine that is registered will be called SOBERANA and it will be ready to vaccinate our entire population sometime in the first six months of 2021.

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