

Phase 2



Participant Handbook

This handbook contains important information about the LEGEND study. Please keep it in a safe place and bring it with you to your study visits.



Study contact information

Study Doctor:

Study Nurse/Coordinator:

Other Contact Telephone Numbers:

Emergency Telephone Numbers:

Welcome to the LEGEND study

Thank you for joining the LEGEND study.

We know the journey with bladder cancer is difficult, and we believe there should be more options before bladder removal. The purpose of the LEGEND study is to test whether the study drug can safely help the body destroy cancer cells and delay or prevent bladder removal for people with non-muscle invasive bladder cancer (NMIBC).

We want you to know what to expect during the study. We also want you to be comfortable with what is asked of you. This handbook covers important information about these topics:

- NMIBC overview
- How the study will work
- Study drug and dosing
- Study tests and procedures
- Important study reminders
- Clinical study participation

There are also blank pages in a notes section in case you want to take notes during study visits.

We appreciate your involvement in this study! If you have any questions, do not hesitate to ask the study doctor or staff.

Sincerely,

The LEGEND study team



NMIBC overview

Non-muscle invasive bladder cancer (NMIBC) happens when cancer cells grow in the tissue that lines the inside of the bladder but do not reach any layers of bladder muscle. The bladder is the organ that holds urine. Its muscles contract to push urine out through the urethra when you urinate. The muscles are under the bladder lining and layers of tissue, so cancer that starts in the lining can eventually make its way into the muscle below.

You qualify for the LEGEND study because you have one of the following stages of bladder cancer that are considered NMIBC because they have not reached the bladder muscle:

Ta	The tumor is growing in somewhat of a lump, towards the hollow center of the bladder.
Tis	The tumor is flat and growing along the lining of the bladder.
T1	The tumor has grown into the tissue just under the lining of the bladder.

Usually, the first step to treating bladder cancer involves surgery to remove the tumor, followed by BCG therapy to reduce the risk of the cancer coming back. BCG, or Bacillus Calmette-Guerin, is an immunotherapy drug infused in the bladder and sometimes used to treat NMIBC. If BCG therapy is not an option or does not work, bladder removal is often recommended. The LEGEND study is designed to find out if the study drug could be a safe and effective option that would allow people at this point in their bladder cancer journey to keep their bladder.

How the study will work

The LEGEND study has 2 phases. Phase 1 is complete. You are enrolled in Phase 2. Phase 1 determined what dose and dosing schedule would be used in Phase 2. Phase 2 will further test how safe and effective the determined dose and dosing schedule are.

The study may last up to 144 weeks (about 2 years and 9 months). You may have up to 1 year of follow-up after your last dose of study drug. The study is divided into the following periods:

Screening

- You have already completed the Screening visit.

Study Drug (up to 144 weeks)

- You will come to the study center to receive at least 1 cycle, and as many as 12 cycles, of the study drug. One cycle is about 12 weeks.
- **Initial Study Drug Period** (Cycles 1 to 4): You will receive the study drug once a week for the first 2 weeks of each cycle and once again in the fifth and sixth week of each cycle.
- **Study Drug Maintenance Period** (Cycles 5 to possibly 12): If the cancer has not come back at the end of the first 4 cycles, you will continue for Cycles 5 to 8. You will receive the study drug once a week for the first 2 weeks of each cycle.
- If the cancer has not come back after 8 cycles, your study doctor may discuss either continuing for 4 more cycles (12 cycles total) or entering the Follow-up Period. If you choose Follow-up, you will have visits every 12 weeks while the cancer has not come back.
- You will have regular study visits for tests and procedures during each cycle.
- You will have a cystoscopy, urine cytology, and/or a bladder biopsy near the end of each cycle to find out the status of the cancer and whether you can continue with the next cycle.
- If the cancer comes back at the end of any cycle, you will not have more cycles. You will have a study visit at Week 12 of your last cycle and follow-up care as described in the next section.

Follow-up (up to 1 year)

- If you stop taking the study drug during the **Initial Study Drug Period** (first 4 cycles), you will have a study visit at Week 12 of your last cycle, a follow-up visit 8 weeks later, and phone calls every 3 months for 1 year.
- If you stop taking study drug during the **Study Drug Maintenance Period**, you will have a study visit at Week 12 of your last cycle and receive phone calls every 3 months until week 96 (end of the first maintenance period).

Study drug and dosing

The study drug is an investigational drug, which means it has not been approved by the US Food and Drug Administration (FDA), or the regulatory authority in any country, to be used outside of clinical research.

The study drug is a type of gene therapy. It includes tiny pieces of DNA, called genes, that are intended to give your immune system new instructions on how to recognize and fight cancer cells. The study drug is a non-viral gene therapy, which means it does not use a modified virus to get into cells and deliver the instructions, like many other gene therapies.

You will receive the study drug as a liquid solution directly into your bladder through a tube called a catheter. The process will take about 60 minutes. Receiving the study drug directly in the bladder, rather than as a pill or infusion into a vein, for example, may prevent extreme side effects that are common with other types of cancer therapy.

Study tests and procedures

The study tests and procedures (summarized in the table) help the study doctor monitor your health and the effects of the study drug.
































STUDY TEST OR PROCEDURE	WHAT TO EXPECT
Physical exam	The study doctor will check your overall health by looking at your head and neck, stomach area, and arms and legs. He or she may also listen to your heart and lungs.
Vital signs	A study team member will measure your blood pressure, heart rate, body temperature, and breathing rate.
Blood & urine tests	<p>A study team member will take samples of your blood and send them to the lab for testing.</p> <p>A study team member will give you a clear, plastic cup and ask you to provide urine that will go to a lab for testing.</p>
Heart test	A study team member will place small stickers on your chest, arms, and legs to measure your heart's electrical activity. This test is called an electrocardiogram (ECG).
Cystoscopy	The study doctor will insert a tool, called a cystoscope, into your urethra. This will allow him or her to see inside your bladder. You may receive some type of anesthesia (numbing medication) so that you do not feel pain during the procedure.
Biopsy	The study doctor will remove a small sample of cancer cells or tissue from your bladder and send them to a lab to find out the status of the cancer. You may receive some type of anesthesia (numbing medication) so that you do not feel pain during the procedure.

STUDY TEST OR PROCEDURE	WHAT TO EXPECT
MRI or CT scan	<p>The study doctor will use magnetic resonance imaging (MRI) or a computed tomography (CT) scan to assess the status of the cancer. You may be given a contrast material, by mouth or by injection, to increase the quality of the images produced by the scans.</p> <p>For an MRI, you will lie on a narrow table that slides into the MRI machine, which will use radio waves and a magnetic field to take images of the inside of your pelvis and stomach area.</p> <p>For a CT scan, you will lie on a narrow table that slides into the CT machine, which will use x-rays to create images of your pelvis and stomach area.</p>
Questionnaires	<p>You will answer questions about your quality of life and experience with cancer and cancer therapies. Questions cover a wide range of topics designed to assess your physical, emotional, sexual, and social health.</p>



Schedule of study tests and procedures













The following tables show when you can expect to receive each test or procedure.

CYCLES 1-4						
	Initial Study Drug Period					Final Cycle Visit
	Day 1	Day 8	Day 29	Day 36	Day 64	Day 78 (of Final Cycle)
	Week 1	Week 2	Week 5	Week 6	Week 10	Week 12 (of Final Cycle)
Test or Procedure						
Physical exam						
Vital signs						
Blood & urine tests						
Heart test						
Study drug administration						
Cystoscopy and/or biopsy						
MRI or CT						
Questionnaires						
Review of medications and symptoms or side effects						

CYLCES 5-12				
	Study Drug Maintenance Period			Final Cycle Visit
Week (after Final Cycle Visit for Cycles 1–4 or 5–8)	Week 1	Week 2	Week 10	Week 12 (of Final Cycle)
Test or Procedure				
Physical exam			🔬	🔬
Vital signs			🔬	🔬
Blood & urine tests			🔬	🔬
Heart test				🔬
Study drug administration	🔬	🔬		
Cystoscopy and/or biopsy			🔬	
MRI or CT				🔬
Questionnaires				🔬
Review of medications and symptoms or side effects	🔬	🔬	🔬	🔬



 **LEGEND**

	FOLLOW-UP*			
	If cancer comes back during the Initial Study Drug Period		If choosing Follow-up instead of optional Study Drug Maintenance Period	
Timeframe	8 weeks after Final Cycle Visit	Every 3 months (phone)	Every 3 months while cancer has not come back	Every 3 months (phone) if cancer comes back
Test or Procedure				
Physical exam				
Vital signs				
Blood & urine tests				
Cystoscopy and/or biopsy				
MRI or CT				
Review of medications and symptoms or side effects				

*Follow-up depends on whether the cancer has come back.

- If the cancer has come back during the Initial Study Drug Period (first 4 cycles), you will have 1 follow-up study visit at 8 weeks after your Final Cycle Visit, and then you will receive phone calls every 3 months for 1 year after your Final Cycle Visit.
- If the cancer has not come back, but you decide not to enter the optional Study Drug Maintenance Period, you may enter optional follow-up. This includes visits every 3 months while your cancer has not come back.
- If the cancer comes back during the Study Drug Maintenance Period or Follow-up, you will receive phone calls every 3 months rather than attending visits, until Week 96.

**Once per year.

Important study reminders

As a study participant, you are expected to do the following:

- Attend all study visits. Let the study team know about any days you may be traveling, on vacation, or busy and not available to visit the study doctor.
- Follow all instructions from the study team.
- Tell the study doctor before taking any new medications during the study, including vitamins, herbal medications, and prescription medications.
- Report any symptoms or medical problems you have during the study.
- Ask the study team any questions or let them know if you need more instruction. Take notes to help you remember what happened between visits and any questions you have for the study doctor or staff.
- Remember that your participation is completely voluntary. You may leave the study at any time for any reason. However, if you decide to leave, we ask that you talk to a member of the study team and go to 1 more visit for final tests and procedures.
- Notify the study team of any changes to your contact information.

Clinical study participation

Clinical research studies help scientists and doctors explore whether a medical strategy, therapy, or device is safe and effective for humans. The data gathered from clinical research has the potential to improve your health and the way you receive medical care. What we learn from the LEGEND study may help those with bladder cancer in the future.

The rules and ethics that doctors must follow to practice medicine also apply to clinical research studies. Additional standards called Good Clinical Practice also apply.

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