

**CURE
HSV**



CURE



TREATMENT



PREVENTION

Herpes Cure Pipeline 3.0





Thank you.



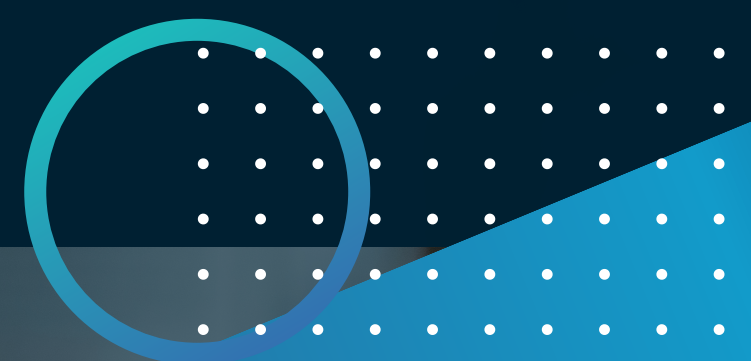
Dear Colleagues,

We're grateful for your support as the leadership at Herpes Cure Advocacy and our volunteer patient task force work expeditiously to change the field for Herpes Simplex Virus.

The Herpes Cure Pipeline 3.0 is a resource for patients and professionals globally – it reflects the momentum in the field and the hope for change.

With hope and gratitude,

Dr. Jeffrey Klausner

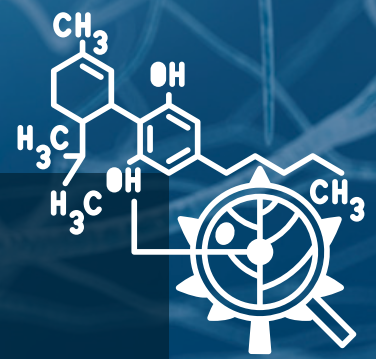


CLINICAL TRIALS 101

PRE-CLINICAL STUDY

Early Discovery and ongoing exploratory research. Before applying for a clinical trial, researchers need to show proof of concept with their idea for a new treatment.

Herpes Cure Advocacy includes projects in the Herpes Cure Pipeline who have expressed intent of entering clinical trials and commercialization of a new treatment, vaccine or cure for Herpes Simplex.



PHASES

PHASE 1: SAFETY AND DOSING

The first step in testing a new treatment in humans. A phase I clinical trial tests the safety, side effects, best dosage and how to administer a new treatment.



PHASE 2: EFFICACY

Phase 2 studies determine the effectiveness of an experimental drug on a particular disease or condition.



PHASE 3: EFFICACY AND MONITORING SIDE EFFECTS

Phase 3 studies typically further study efficacy, in larger groups of people, for a longer period of time before receiving final approval to come to market.



LEGEND

PRE

Pre-Clinical Research

1

Phase 1

2

Phase 2

3

Phase 3

KHSV

Herpes Keratitis

HSV-1

Herpes Simplex Virus
Type 1

HSV-2

Herpes Simplex Virus
Type 2



THERAPEUTIC VACCINE

A therapeutic vaccine is a vaccine which is administered after a disease or infection has already occurred. A therapeutic vaccine works by activating the immune system of a patient to fight an infection.



PROPHYLACTIC VACCINE

Vaccines to prevent or ameliorate the effects of a future infection. Some vaccines offer full sterilizing immunity, in which infection is prevented completely.



GENE EDITING

Genome editing, or genome engineering, or gene editing, is a type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome of a living organism.



ANTIVIRALS AND IMMUNOTHERAPIES

Antivirals are medications that help your body fight off certain viruses that can cause disease. Antiviral drugs are also preventive. AVTs can block receptors so viruses can't bind to and enter healthy cells, boost the immune system, helping it fight off a viral infection, or lower the viral load (amount of active virus) in the body.



PIPELINE 3.0

By Category



Gene Editing

Fred Hutch Cancer Research Center
Excision Biotherapeutics
Shanghai BD Gene



Prophylactic Vaccines

BioNtech @Upenn
Rational Vaccines
X-Vax
Blue Willow
Thyreos Vaccines

Phase I



Therapeutic Vaccines

GSK
Eurocine
Moderna
Rational Vaccines
Simplexia



Antiviral and Immunotherapies

Aicuris
Assembly Biosciences
Heidelberg Immunotherapeutics
Innovative Molecules
Kimer Med
Squarex
Symbio Pharma
United Biopharma



PIPELINE 3.0

By Phase



Preclinical

- Assembly Biosciences
- Blue Willow
- Excision Biotherapeutics
- Eurocine
- Fred Hutch Cancer Research Center
- Kimer Med
- Rational Vaccines
- Symbio Pharma
- Simplexia
- Thyreos Vaccines
- X-Vax

Phase 1

- BioNtech @Upenn
- GSK (1+2)
- Innovative Molecules
- Moderna (1+2)
- United Biopharma

Phase 3

- Aicuris

Phase 2

- Squarex
- Shanghai BD Gene
- Heidelberg Immunotherapeutics





Welcome to the latest clinical pipeline for Herpes Simplex Virus types 1 +2, the Herpes Cure Pipeline 3.0. Here we've updated, removed, and added new projects (preclinical research and in-human clinical trials) that have occurred over the last year, since the 2.0 edition was published.

New companies added to the pipeline this year are: **Assembly Biosciences, GSK, Kimer Med, Moderna, Simplexix, Symbio Pharma,** and **Thyreos Vaccines. Assembly Biosciences, Kimer Med** and **Symbio Pharma** are all small to mid-sized companies developing new antiviral therapies. Antiviral drugs are designed to inhibit the replication of the herpes simplex virus (HSV), similar to acyclovir and valacyclovir. The goal for these companies is to produce new antivirals that are more effective in reducing shedding and outbreak frequency than current on-the-market medications. Conversely, **Simplexix** and **Thyreos** are investigating therapeutic and prophylactic vaccines, respectively, that target the immune system, rather than the virus itself. A therapeutic vaccine is designed to reduce shedding and outbreak frequency long-term in those already infected with HSV. A prophylactic vaccine is designed to prevent HSV from establishing latency altogether in those not infected with HSV. All these new projects are in the pre-clinical research phase in anticipation of clinical trials for a new treatment for HSV-1 and HSV-2.

Assembly Biosciences is working on IND enabling studies and preparing for clinical trials in the United States during the first half of 2024. **Assembly Biosciences** has two projects for HSV in their pipeline, ABI-5366 is long-acting HSV helicase-primase inhibitor, a small molecule approach that is expected to enter clinical trials early 2024. The second pre-clinical research project, an oral pan-herpes non-nucleoside polymerase inhibitor (NNPI) with broad spectrum antiviral capability that is at an earlier stage of development than ABI-5366.

Kimer Med, based out of New Zealand, is working on the development of another broad spectrum antiviral. They have already shown success in vitro against viruses with plans to test the compound against HSV in due time. **Simplexix**, based in Sweden, has developed an HSV-2 vaccine candidate that is currently being tested in mice through preclinical trials. The project is based on work performed at the University of Gothenburg in Sweden. The vaccine antigen is derived from a virus surface glycoprotein from HSV-2 and is presented as an adjuvanted purified recombinant protein to induce an immune response.

Thyreos is not new to herpes vaccine research as they currently have vaccines approved for use in animals, including livestock, horses and chickens. Based in Lincoln, Nebraska, Thyreos was founded to develop a new class of live-attenuated herpesvirus vaccines that include prophylactic and therapeutic vaccines for HSV-1 and HSV-2. As opposed to traditional weakened live-attenuated designs, **Thyreos** vaccines are specifically made non-neuroinvasive. In so doing these vaccines uniquely retain full capacity to elicit robust immune responses in mucosal tissues, while eliminating concerns of vaccine complications in the nervous system. In May 2023 **Thyreos** closed a \$1 million series seed b round of financing and has been awarded a \$1.6 million NIH NIAID STTR Fast-Track grant for preclinical development and study of an HSV-2 non-neuroinvasive live-attenuated vaccine based on Thyreos R2[®] technology.

Symbio Pharma, based in Tokyo and established in 2005, is another new entry to the pipeline this year. **Symbio Pharma** owns the license for Brincidofovir, sold under the brand name Tembexa, an antiviral drug used to treat smallpox that is already on the market in the United States and the European Union. Symbio Pharma is studying Brincidofovir against other pathogens in hopes of expanding the indication of this treatment to other viruses including HSV.



There are a number of companies testing new vaccines and antivirals in human clinical trials. **GSK**, **BioNTech**, and **Moderna** have all begun clinical trials on therapeutic and prophylactic vaccines since the last time the Pipeline was published. Moreover, additional industry clinical studies are underway with several German-based programs with new antivirals and small molecules, such as **AiCuris**, that is estimated to come to market first with their highly anticipated antiviral therapy, Pritelivir, for acyclovir-resistant HSV. Following close behind them is **Innovative Molecules**, that is investigating a novel antiviral compound called IM-250, which has shown in preclinical work to possibly affect the latent virus. The company has announced that Phase 1 trials have already commenced. Lastly, **Heidelberg Therapeutics** has completed Phase 2 trials on a novel monoclonal antibody therapy that has the potential in serving as a long-acting medication for HSV-1 and HSV-2. Results were negative. **Shanghai BDgene** is a Chinese company spun off from Shanghai Jiaotong University that is pioneering a novel gene therapy to not only treat, but to possibly cure HSV-1 keratitis with Phase 2 trials already completed.

GSK announced clinical trials soon after the publishing of the Pipeline 2.0, and given the company's track record, there is reason for hope. In 2017, **GSK** released the therapeutic vaccine for herpes zoster (shingles) called Shingrix, which boasts a 91-97% efficacy in preventing zoster outbreaks. The success of this recombinant protein vaccine is tied to its highly effective adjuvant, AS01-B, which is designed to supercharge the cellular and humoral immune response towards zoster. In their current Phase 1/2 clinical trials for HSV, GSK is also testing a similar recombinant protein vaccine with an adjuvant as a therapeutic for those already infected with HSV. The company has shown confidence in the trials by actively posting job openings for positions related to Phase 4 development of this therapeutic vaccine for HSV. Phase 4 occurs after a drug is released on the market. Because of GSK size, pace of progress, and success with the Shingrix vaccine for herpes zoster, patients are optimistic.

In December 2022, **BioNTech** dosed the first patient with their BNT163 prophylactic herpes vaccine candidate. The vaccine candidate is meant to prevent HSV-2 and potentially HSV-1. This work is in partnership with Dr. Harvey Friedman and his team at the University of Pennsylvania. Dr. Friedman is also conducting preclinical studies (in partnership with Shionogi) for a therapeutic vaccine using an adjuvant provided by Shionogi. It is important to note that in May 2020, Shionogi entered a material transfer agreement with now-defunct Genocea to develop and commercialize the GEN-003 vaccine, an adjuvanted therapeutic vaccine for HSV-2 that showed 65-69% efficacy in Phase 2 trials in 2017. Clinical trials on the Friedman-Shionogi therapeutic vaccine are currently pending until preclinical studies are completed.

In September 2023, **Moderna** announced a new Phase 1/2 clinical trial on a therapeutic mRNA vaccine for those infected with HSV-2. The trials are analyzing shedding rates and outbreak frequency 6 months and 12 months after the second injection of the vaccine is given to patients. The company has stated in press releases that it hopes the vaccine is just as effective, if not more, than current antiviral therapies available to patients. Due to their success in developing a highly effective COVID vaccine and the novelty of the mRNA technology, there is hope that their current trials will yield positive results.

Already in Phase 3 trials, **AiCuris** continues to be the leader in bringing a new treatment to market for those with HSV. The last time a new treatment was approved was in 1995, with the release of valacyclovir. Pre-launch planning is currently underway in the US and globally - reflected by changes in the organizational structure with a new US-based CEO. AiCuris continues to invest in this disease with high unmet need and have recently begun pre-clinical studies for an intra-vaginal ring as a therapeutic for HSV-2.



Shanghai BD Gene has made waves in the HSV research community with their successful Phase 1/2 trials that ended summer of 2022. The approach, an HSV-1-erasing lentiviral particle (referred to as HELP), was shown in these pre-clinical studies to significantly block HSV-1 replication and eliminate the viral reservoir in the ganglia. In this trial, 3 patients with HSV-1 keratitis were treated once with their novel gene therapy, BDIII, to remove the latent virus. After one month of treatment, each patient tested negative via Igg for HSV-1. Over the following 18-month monitoring period, each of the 3 patients continued to test negative for HSV-1 with no detection of the virus occurring. The company has been reluctant in calling this a cure and instead has opted to designate it as a treatment. However, the more time passes with each patient continuing to test negative, the more support there will be to view this therapy as curative. Furthermore, the company submitted and received approval for orphan drug designation of BDIII from the US FDA and has also received IND approval to begin clinical trials in the United States in the near future. Lastly, the company has HSV-2 in their pipeline, indicating that there are plans to test this potentially curative gene therapy on those infected with HSV-2.

Rational Vaccines also continues to progress its preclinical research of rationally engineered, live attenuated viral immunotherapeutic and prophylactic vaccine candidates targeting HSV-1 and HSV-2 infections. The company currently has several vaccine candidates in the pipeline and was recently awarded \$2.8 million in National Institute of Health (NIH) funding to help further its research. RVx received three separate grants. The first for a diagnostic test, the second is a live-attenuated HSV-1 strain meant to prevent and treat ocular herpes, and the third is the development and manufacturing of a prophylactic and therapeutic HSV vaccine. This technology is based on the pioneering research of the late Dr. William Halford.

Based in San Francisco, **Excision Bio** are currently in clinical trials for EBT-101 (their CRISPR-based technology for the treatment of HIV) but also have HSV (EBT-104) in their clinical pipeline. This team is actively fundraising to continue to advance their research in this therapeutic area in anticipation of clinical trials. EBT-104 is CRISPR-based gene editing therapy; Cas9 delivered by AAV to make a dual cut in the viral genome to prevent viral replication. Excision BioTherapeutics, Inc. is a clinical-stage biotechnology company developing CRISPR-based therapies as potential cures for viral infectious diseases. Excision's technology combines CRISPR (developed by Dr. Jennifer Doudna in UC, Berkeley) with a novel gene editing approach (Dr. Kamel Khalili at Temple University) for a unique curative approach to viral infection.

Drs. Keith Jerome and Martine Aubert, two virologists at the **Fred Hutch Cancer Research Center**, and their team have been pioneering a new gene therapy to cure HSV-1 and HSV-2 using adeno-associated virus (AAV) with meganucleases (rather than CRISPR) as the gene editor. In 2020, they published a ground-breaking study on how this novel gene therapy removed up to 95% of the latent virus in mice. Since that time, Dr. Jerome and his team have focused this gene therapy on removing the latent virus of HSV-1 and HSV-2 in guinea pigs, with plans to move to human trials in the near future. In an update last year, Dr. Jerome's team provided a preliminary update on the guinea pig trials in which 30% of the latent virus was removed. This corresponded with an approximately 50% reduction in outbreak frequency and shedding. This illustrates that complete removal of the latent virus is likely NOT required to eliminate outbreaks and shedding. Dr. Jerome has stated that his team is aiming to remove at least 90% of the latent virus in guinea pigs before moving to human trials. In October 2023 the **Fred Hutch Cancer Research Center** team and Jerome Lab announced that clinical trials are on the horizon.



Gene Editing












Organization	Research Focus	Approach	Current stage	Notes
<u>Fred Hutch Cancer Research Center</u>	HSV-1 HSV-2	Sterilizing Cure In-vivo gene-editing therapy to eliminate the latent HSV-1 and HSV-2 in sensory ganglia.	PRE	97%+ removal of virus in mice and 30% from the guinea pigs. Pre-clinical ongoing.
<u>Excision BioTherapeutics EBT-104</u>	HSV-1 HSV-2	Therapeutic CRISPR-based gene editing therapy (gRNA); Cas9 delivered by AAV or non-viral vectors to make a dual cut in the viral genome to prevent replication	PRE	Pre-clinical ongoing
<u>Shanghai Bdgene Co. BD-111</u>	KHSV	Sterilizing Cure CRISPR-based gene editing cure to treat refractory HSV-1 keratitis (i.e., corneal infection of the eyes.)	1 2	Three people dosed in human clinical trials completed in China.
<u>Shanghai Bdgene Co. BD-111</u>	HSV-2	Sterilizing cure CRISPR-based gene editing cure to treat genital HSV-2	PRE	Pre-clinical ongoing.



Therapeutic Vaccines



Organization	Research Focus	Approach	Current stage	Notes
<u>GSK</u> <u>GSK3943104A</u>	HSV-2	Functional Cure Recombinant protein - adjuvanted vaccine	 Recruiting Now  	Combined Phase 1+2 trials recruiting now. Expected to finish in 2025.
<u>Eurocine</u>	HSV-2	Sub-unit vaccine (T-cell based antigen engineering) mRNA & protein		Pre-clinical ongoing. This is the vaccine that was initially developed by Redbiotech.
<u>Moderna</u> <u>mRNA-1608</u>	HSV-2	Therapeutic Vaccine mRNA w/cross protection against HSV1	 Recruiting Now  	Combined Phase 1+2 trials recruiting now. Expected to finish 2024.
<u>Rational Vaccines</u> <u>RVx-201</u>	HSV-2	Live attenuated virus		Received Innovation Passport in UK Expected 2024
<u>Simplexia</u>	HSV-2	gG-2 protein		NEW Pre-clinical ongoing This specific protein is glycoprotein G-2 (gG-2), which only elicits antibody and T-cell reactivity to HSV-2 and not to HSV-1.










Prophylactic Vaccines



Organization	Research Focus	Approach	Current stage	Notes
<u>Rational Vaccines</u> <u>RVx-1001</u>	HSV-1 HSV-2	Live attenuated (weakened) virus vaccine	PRE	Received Innovation Passport in UK Expected 2024
<u>X-Vax Technology</u> <u>Delta gD-2</u>	HSV-1 HSV-2	Vaccine with HSV2 genetically deleted for glycoprotein-D	PRE	Expected to enter clinical trials 2024
<u>BioNtech / UPenn</u> <u>BNT163</u>	HSV-2	mRNA vaccine	1  Recruiting Now	Clinical trials recruiting now.
<u>Blue Willow</u> <u>NE HSV-2</u>	HSV-2	Intranasal vaccine using nanoemulsion adjuvant	PRE	Status of pre-clinical unknown.
<u>Thyreos Vaccines</u> <u>R2</u>	HSV-2	Non-neuroinvasive live-attenuated vaccine	PRE	NEW Pre-clinical ongoing

Antiviral and Immunotherapies



Organization	Focus	Approach	Current Stage	Notes
<u>AiCuris</u> Pritelivir - AIC316	HSV-2	Anti-viral, Helicase-Primase inhibitor	 Recruiting Now 	In Phase 3 Clinical trials, Pritelivir is the project in the pipeline that is closest to commercialization. Currently being studied for immunocompromised patients.
<u>Assembly Biosciences</u> ABI-5366	HSV-1 and HSV-2	Long-acting herpes simplex virus type 2 (HSV-2) helicase inhibitor. Small molecule.		NEW IND enabling studies in progress. Targeting initiation of clinical trials 1H 2024.
<u>Heidelberg Immuno Therapeutics</u> HDIT101	HSV-2	Intravenous infusion of Monoclonal antibody		Results available on ClinicalTrials.gov
<u>Heidelberg Immuno Therapeutics</u> HDIT101	HSV-1	Monoclonal antibody Topical formulation for orolabial lesions		Phase 2 Active
<u>Innovative Molecules</u> IM250	HSV-2	HSV Helicase-Primase inhibitor, small molecule	 Recruiting Now 	Phase 1 clinical trial K793 recruiting now in Germany.



Antiviral and Immunotherapies



Organization	Focus	Approach	Current Stage	Notes
<u>Kimer Med</u> <u>Vtose®</u>	HSV-2	Broad spectrum antiviral	PRE	NEW Pre-clinical ongoing in NZ. Good results against another virus. Initiation of clinical trial expected 2025.
<u>Squarex</u> <u>SADBE</u>	HSV-1 HSV-2	Topical immunomodulator	2	Fundraising for Phase 3 SADBE is a topical immunomodulator applied on inner upper arm in order to suppress outbreaks.
<u>United BioPharma</u> <u>UB621</u>	HSV-2	Subcutaneous injection of Monoclonal antibody	2	Three Phase two trials are planned with focus on different targets

RECRUITING

CLINICAL TRIALS FOR HERPES AS OF Q2 2023

✓ AiCuris

✓ BioNtech

✓ GSK

✓ Heidelberg
Immunotherap
euteic

✓ Innovative
Molecules

✓ Moderna

✓ United
Biopharma

**Check your eligibility
and apply for clinical
trials:**

 U.S. National Library of Medicine
ClinicalTrials.gov

Results from Phase 2 for HSV-2 posted.
HSV-1 Trial is active - not recruiting.

Planned - not yet
recruiting.

SILENT NO MORE






**CURE
HSV**



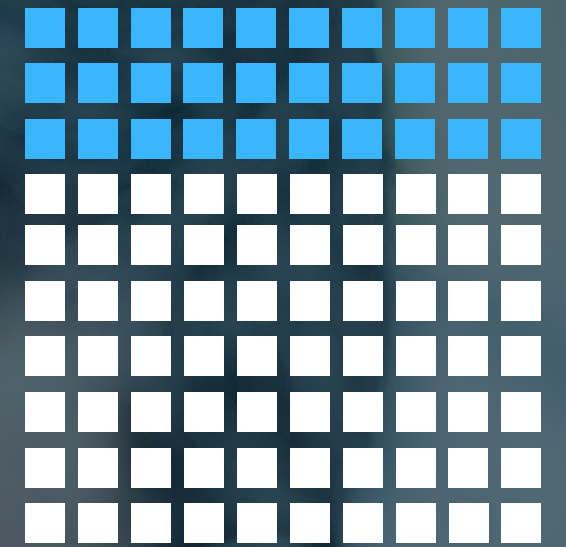
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**SILENT
NO
MORE**

**We need a cure today.
Because patients are waiting.**

