Preventing Oral Herpes Outbreaks

Developing Options for Not Just Treating, But Preventing, Outbreaks of Herpes Labialis (Cold Sores or Oral Herpes)

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SUMMARY

50% of the global population is infected with HSV-1, also known as "herpes labialis" or "oral herpes."

Squarex, LLC, *(St. Paul, MN) has recently completed Phase II clinical trials for its drug formulation SQX770, a topical drug applied to the skin of the arm. Unlike current treatments, SQX770 actually* ***prevents*** *cold sores in people who have frequent outbreaks. SQX770 is the only drug that prevents cold sores. One dose gives protection for 3-months or more, potentially making painful, unsightly, and embarrassing sores a thing of the past. Unlike existing drugs that only treat outbreaks, SQX770 can be given at any time—between outbreaks or at any time during an outbreak. Existing drugs must be given within hours of onset of the first tingle and have no effect on preventing future outbreaks.. SQX770's mechanism of action is to simply improve the body's own immune response by shifting the immune response from antibodies to T cells. That means it is likely to work for other viral diseases, in particular genital herpes and maybe other diseases.*

The drug is administered topically to the arm (not to the lip or face), eliminating risk of adverse events on the face, and one dose acts for three months or more.

US Patent N0. 10.744.084, 10.245.314, US Patent pending No. 16/259.922, 16/932.11, Foreign Patent application No. 10.245.314

BACKGROUND

Herpes labialis, also known as cold sores or oral herpes, is caused by a herpes simplex virus (HSV) infection of the lips, mouth, or gums, or areas surrounding the lip, including the nose or edge of the nostrils. It manifests as lesions characterized by redness, pain, swelling, and often ulcers, located usually at the vermillion border of the lip, less often other areas of the lip, the nostrils, or mucous membranes of the mouth or gums.

Most cases of herpes labialis are caused by HSV type 1 (HSV-1) and most cases of genital herpes are caused by HSV-2, but HSV-2 causes a significant fraction of oral herpes cases and HSV-1 causes a portion of genital herpes cases. In our latest clinical trial in persons who reported they had 4 or more herpes labialis outbreaks in the prior 12 months, 54% of patients were positive for antibodies against HSV-1 but not HSV-2, 32% positive for both, and 6% positive for HSV-2 only.

Approximately 50% of the population of the U.S. and the rest of the world has been infected with HSV. Most people are infected by age 20, and probably most of those as infants. One endearing theory is that most people are infected as infants by being kissed by their parents.

Children and adults can also be infected by sharing glasses or utensils, among other means. The best study on the prevalence of outbreaks was a population survey in France, which found 15% of the population had at least one episode of herpes labialis in the prior 12 months and 2.1% had 6 or more outbreak episodes in the prior 12 months (Stalder et al.).

Primary oral infection with the herpes simplex virus typically occurs at a young age. It is usually asymptomatic, and is not associated with significant morbidity. After primary oral infection, HSV-1 may persist in a latent state in the trigeminal ganglion, a nerve in the face, and later reactivate as herpes labialis, or "cold sores." The virus migrates along nerves in the face to the lip or other areas near the lip and causes the lesions there. Common triggers for reactivation are well known and include ultraviolet light, trauma, fatigue, stress, fever, inflammation, and menstruation.

HSV-1 lesions or sores affect up to 45 percent of the U.S. population. They classically manifest as a well-localized cluster of small vesicles along the vermilion border of the lip or adjacent skin. The vesicles subsequently rupture, ulcerate, and crust within 24 to 48 hours. Spontaneous healing occurs over four to ten days. Cold sores are associated with significant pain and itching, and the redness and open sores on or near the lip are embarrassing.

SQUAREX's SQX770 CLINICAL TRIALS: PREVENTION IS POSSIBLE!

Squarex's SQX770 formulation has successfully completed three human clinical trials, and <u>all three</u> have shown significant efficacy for the indication of *preventing future HSV-1 outbreaks* in people who have frequent outbreaks. This is exciting given that all current approved drugs only address outbreaks *after* they happen. There is no prophylactic on the market (either OTC or prescribed).

SQX770 acts by a different mechanism of action than any existing drug—it simply improves antiviral immune function, much like a vaccine, except it is not specific for HSV-1. Its dosing is also unique and more convenient than any approved drug. It is applied topically, but to a patient's arm, not to the lip or face, and only applied once every three months. And it can be applied any time—between outbreaks or at any time during an outbreak—whereas all the approved drugs must be dosed within hours of the first sign of a tingle during an outbreak.

Arm application mitigates the major side effect of the drug: a rash at the application site involving redness and occasionally mild pain and itching (although significantly less pain and itching than a cold sore episode). Redness, pain and or itching on the the arm is a far better alternative to the lips/face.

CLINICAL TRIAL SUMMARY

<u>Phase 1 (Reference (3)</u>

Double-blind placebo-controlled study, conducted at Massachusetts General Hospital, associated with Harvard University, in 44 patients, 15 receiving placebo and 29 receiving SQX770. The patients were people who reported they had 6 or more herpes labialis outbreaks in the prior 12 months. After one dose to the arm, median time to next outbreak was 40 days in the placebo group

versus greater than 124 days in the SQX770 group, and that difference was highly significant (P<0.01, meaning less than a 1% possibility the difference was due to random chance.)

There was a suggestion in the data that it took 21 days or more for the drug to exert its effect. There was no difference between the two groups in outbreaks in the first 21 days but then the treated group was much less likely to have an outbreak after 21 days or so.

Phase 2 (Reference (4))

Double-blind placebo-controlled study, conducted at **Stanford University, Massachusetts General Hospital,** and three other commercial clinical sites in 140 patients. The greatest efficacy of SQX770 was in days 43-121 after the single dose, which was expected because based on the first clinical trial and the mechanism of action we knew it took about three to six weeks after dosing for the immune system to respond, just as it takes for vaccines. Tapering of efficacy over time was also expected; in other words, the drug might become less effective three to four months after a dose. Over days 43-121, the patients receiving one dose of SQX770 had significantly longer time to next outbreak (2.4 fold longer than placebo (P=0.02) and significantly fewer outbreaks (2.6-fold fewer outbreaks versus the placebo group (P<0.01)). In addition to being fewer, the outbreaks in the treated group were also *significantly less severe* than the outbreaks in the placebo group (average severity on a 0-3 scale 0.4 in the treated group versus 1.4 in the placebo group (P=0.01).

- 2.4-fold longer time to next outbreak (P=0.02)
- 2.6-fold fewer outbreaks (P<0.01)
- The outbreaks were significantly less severe. On a 0-3 scale, average severity score of 0.3 vs. 1.4 (P=0.01)

Mechanism of action clinical trial (Reference (5))

The aim of this clinical study was to determine the mechanism of action of SQX770 and the immune parameters that correlate with fewer cold sore outbreaks or better control of the HSV virus. Participants were all positive for antibodies against HSV-1, so they had all been infected with HSV-1. However, some had frequent outbreaks and others did not, and one purpose of the study was to identify the immune function differences between those with frequent outbreaks and those who had few or no outbreaks. There were three groups of participants, 12 participants in each group:

- Zero outbreaks in the prior 12 months
- 1 or 2 outbreaks in the prior 12 months
- 6 or more outbreaks in the prior 12 months

Blood was collected from each group and researchers isolated the white blood cells and measured immune parameters of how they responded to HSV-1 virus in vitro (in the lab) and measured various immune parameters including immune gene expression.

Subjects with few outbreaks (0-2) or good immune control of the virus differed from those with 6 or more outbreaks and poor immune control of the virus, in these ways:

- More immune cell proliferation to the virus
- Lower anti-HSV-1 antibody levels (significant)
- Higher interferon gamma gene expression when exposed to HSV-1 (significant)

- Lower interleukin-5 gene expression when exposed to HSV-1 (significant)

Interferon gamma is considered the key antiviral cytokine. High levels of it are also linked to better outcomes from COVID-19 disease. It promotes T cell function and is a type 1 cytokine. Type 1 cytokines promote a T-cell immune response or cellular immune response, over a B-cell or antibody immune response.

Interleukin-5, in contrast, is a type 2 cytokine, which promotes antibody production. All of these pieces of evidence indicate that for good immune control of HSV-1 a cellular or T cell immune response (or type 1 immune response) *is preferable* to an antibody or B-cell or type 2 immune response. This fits with a lot of evidence that a cellular immune response and a type 1 immune response is protective against infectious disease in general and viral disease, in particular; whereas antibody responses are less protective.

Effect of SQX770 was simply to improve immune function.
Patients with 6 or more reported outbreaks were given one dose of SQX770. Their blood was collected immediately before dosing and at two weeks and eight weeks later, and the immune assays were repeated as above. Two weeks after dosage, there was little change. But 8 weeks later, there were dramatic changes. All of those changes were in the direction of making this group more like the people with few cold sore outbreaks. Specifically, they had:

- More immune cell proliferation to the virus
- Lower anti-HSV1 antibody levels
- Higher interferon gamma gene expression when exposed to HSV-1 (significant)
- Lower interleukin-5 gene expression when exposed to HSV-1 (significant)

The changes in interferon gamma and interlukin-5 gene expression, which indicate the type-1 to type-2 immune ratio, were particularly dramatic and significant. This ratio, which had been significantly *lower* than in the people with 0-2 outbreaks per year before dosing once with SQX770, 8 weeks after dosing was *significantly higher than the ratio in the healthy people* who had few or no outbreaks. SQX770 made the immune function of those with frequent outbreaks actually *better* than that of those with few or no outbreaks!

SQX770 simply improves anti-viral immune function in people with frequent cold sore outbreaks. That probably has benefit outside of HSV and cold sores.

APPROVED MEDICATIONS CURRENTLY ON THE MARKET (THE COMPETITION)

A few medications have been approved by the U.S. Food and Drug Administration (FDA) to treat cold sores. Approval for treatment means the drugs are to be given during an outbreak to reduce the duration of the outbreak. All of the approved drugs for treatment should be taken as early as possible in the prodrome stage at the first sign of a tingle, before an open sore or even redness develops. Even then, they have modest efficacy of only reducing the duration of an outbreak by a day or so.

No medications are approved to prevent future outbreaks, as SQX770 does.

The drugs listed below are related compounds that are nucleoside analogs that inhibit the DNA polymerase of HSV-1. The best of these and the most widely used is Valtrex®.

Valacyclovir (VALTREX®) tablet:

- Dosing: Oral. Two doses of 2 grams taken 12 hours apart at the first sign of a tingle.
- Efficacy: Reduces duration of outbreaks "about 1 day" versus placebo. No effect on severity of outbreaks. Not approved and no claim of preventing outbreaks with continuous dosing.

Comparison of SQX770 for *preventing* cold sore outbreaks to Valtrex®, the best currently approved drug for *treating* cold sore outbreaks.

	VALTREX® (Valacyclovir)	SQX770 (squaric acid dibutyl ester)
Indication	Treatment: Reducing the duration of a single treated herpes labialis episode	Prevention: Reducing the frequency and/or severity of future herpes labialis episodes
Mechanism of action	Inhibits HSV polymerase to specifically inhibit HSV replication.	Shifts immune function from a type 2 or antibody immune response to a type 1 or cellular immune response. Improves general antiviral immune function.
Dosing	2 grams, orally, twice in one day. Must be given as early as possible in an episode, preferably in the first hours, at the first sign of tingling or symptoms of a herpes labialis episode.	Topical to the arm (not to the lip or a lesion) once every 3 months. Can be given any time—during or between herpes labialis episodes.
Duration of episodes	Reduces by 1 day (from about 5 days to about 4 days)	Not studied yet.
Frequency of episodes	No effect.	2.6-fold reduction in frequency versus placebo.
Severity of episodes.	No effect. Prescribing information says: "No significant difference was observed between subjects receiving VALTREX or placebo in the prevention of progression of cold sore lesions beyond the papular stage."	Significant reduction in severity, from 1.4 in placebo group to 0.3 in treatment group on a 0-3 scale.

Other Top Prescription Competitors in the Space.

Drug name	Mechanism of action	Initiation of dosing	Dosing form	Dosing schedule	Efficacy vs. placebo (in all cases only effective if taken at first sign of a tingle)
Valacyclovir (VALTREX®)	Nucleotide analogue that inhibits HSV viral DNA polymerase.	Immediately when feeling first sign of tingle.	Oral tablet	Twice 12 hours apart.	"About 1 day" faster healing

Acyclovir (ZIVORAX®) tablet	same	same	Oral tablet	Five times per day for five days.	No data
Acyclovir (ZIVORAX®) cream	same	same	Topical, applied to lip or lesion	Five times per day for four days	4.5 days vs. 5 days for placebo.
Penciclovir (DENAVIR®) cream	same	same	Topical, applied to lip or lesion	Every 2 hours while awake for four days	4.5 days vs. 5 days for placebo
Famciclovir (FAMVIR®) tablet	same	same	Oral tablet	Once	4.4 days vs. 6.2 days for placebo
Acyclovir + hydrocortisone (XERESE®) cream	same, plus hydrocortisone as antiinflammatory	same	Topical, applied to lip or lesion	Five times per day for five days	Same as acyclovir cream. Also slightly reduces likelihood of ulceration of lesion (58% vs. 65% for acyclovir cream alone, not statistically significant
Docosanol (ABREVA®) cream	Appears to interfere with fusion of the HSV envelope and host cell membranes, thereby preventing HSV entry into host cells and subsequent viral replication	same	Topical, applied to lip or lesion	Five times per day for up to 10 days.	4.1 days vs. 4.8 days for placebo.

All of the current approved drugs must be taken within hours of the first sign of a tingle in order to be effective. If taken later they seem to have no efficacy. Practically speaking, that means HSV-1 sufferers have to already have the drug on hand. By the time a patient gets a doctor's appointment, or even calls a doctor for a prescription, the doctor sends the prescription to the pharmacy, and the prescription is picked up, likely at least 6 hours have passed and it is already less effective. If a day has passed it probably has no efficacy. Even the time to get to a pharmacy to buy the one drug available without a prescription, docosanol cream, could be an important delay that decreases efficacy.

All of the approved drugs except docosanol cream act by the same mechanism of action of inhibiting the viral DNA polymerase to inhibit HSV virus replication. Docasanol appears to inhibit fusion of the HSV envelope with cell membranes to inhibit virus spread.

The efficacy of all is similar, reducing time of healing of lesions by a day or less, from about 5 days for placebo to 4 to 4.5 days for drug treated patients, and, again, even this mild efficacy is dependent on taking the drug immediately after the first sign of tingling that a cold sore episode is coming on. None are approved or claim any effect in preventing future outbreaks. None have been

shown to significantly reduce the severity of outbreaks or the likelihood they will progress from a tingle to a papule (red, swollen skin) to a vesicle (fluid-filled sore) to an ulcer (open sore).

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