

HspE7 Treatment of Pediatric Recurrent Respiratory Papillomatosis (RRP): Interim Results of an Open-Label Trial

Craig S. Derkay, M.D., F.A.A.P., F.A.C.S., Eastern Virginia Medical School, Norfolk, VA

Jim Arnold, M.D., Rainbow Babies and Children's Hospital, Cleveland, OH

Charles Bower, M.D., University of Arkansas for Medical Sciences, Little Rock, AR

John McClay, M.D., University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Richard J. Smith, M.D., University of Iowa Hospital and Clinics, Iowa City, IA

Jo-Anne van Burik, M.D., Fairview University Medical Center, University of Minnesota, Minneapolis, MN

Brian J. Wiatrak, M.D., F.A.A.P., F.A.C.S., Children's Hospital of Alabama, Birmingham, AL

Daniel Wohl, M.D., Nemours Children's Clinic, Jacksonville, FL

Bruce Berger, M.D., Stressgen Biotechnologies, Collegeville, PA

John R. Neefe, M.D., Stressgen Biotechnologies, Collegeville, PA

Abstract

Background

HspE7, a recombinant fusion protein of Hsp65 from *M. bovis*-BCG and E7 protein from HPV-16, is under development for treatment of HPV-related diseases such as RRP. HPV types 6 and 11 are the most frequent cause of RRP.

Methods

An open-label, single-arm intervention study was conducted in 8 university-affiliated medical centers. 27 male and female patients (pts) with RRP, ages 2–18, were enrolled and followed up to 60 weeks. After a baseline debulking surgery, pts received HspE7 500 mcg subcutaneously monthly, 3 doses over 60 days. The primary endpoint was the proportion of pts who achieved doubling of the first intersurgical interval after the last debulking surgery in the drug treatment period compared with the median intersurgical interval of four surgeries prior to treatment. This endpoint was chosen because spontaneous doubling is unexpected in RRP pts. RRP scale scores, physician/patient global assessments, length of intersurgical interval, and safety assessments were secondary outcome measures.

Results

8 of 27 pts achieved a doubling of the first intersurgical interval. The mean (\pm S.D.) pretreatment intersurgical interval for the entire cohort was 55.3 \pm 24.0 days, compared with 95.6 \pm 81.3 days after treatment (paired t-test $p = 0.0098$), a mean increase of 78.6% (t-test = 0.015). The mean annualized number of surgeries was reduced by 37% after treatment (8.7 \pm 4.2 vs. 5.9 \pm 5.4 procedures, t-test $p < 0.0001$). The most common adverse events were mild to moderate injection-site reactions.

Conclusions

This is the first report of efficacy in RRP with a therapeutic vaccine.

Recurrent Respiratory Papillomatosis (RRP)



Characterized by benign, virally induced wartlike tumors of the larynx and respiratory epithelium that often threaten to obstruct the airway, RRP is a potentially devastating disease whose etiology has been ascribed to specific types of Human Papillomavirus (HPV). By definition, RRP is recurrent, and in many patients it is a grueling, prolonged condition that generates a high level of morbidity and significant mortality for three reasons: the location of space-taking lesions in a very small but vitally important anatomic space, intractable resistance to treatment, and relentless recurrence. Moreover, the course may be complicated by progression and/or malignant transformation. HPV types 6 and 11 are the most frequent cause of RRP.

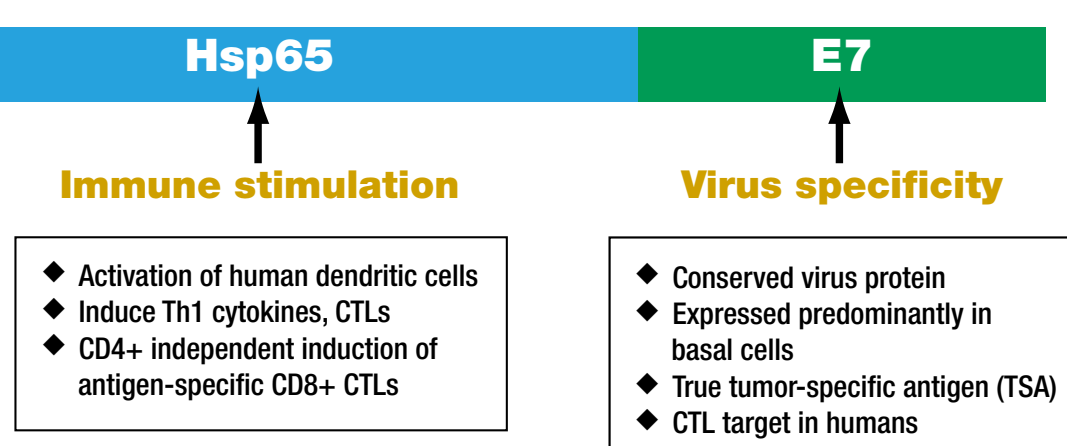
Laryngoscopic view of papilloma filling the endolarynx

Study Drug: HspE7 (SGN-00101)

- ◆ A recombinant fusion protein (CAS# 295371-00-5) expressed in *E. coli*, consisting of the heat shock protein Hsp65 of *Mycobacterium bovis* var. BCG, linked by a single histidine residue at its C terminus to the E7 protein of HPV 16. Clinical activity has been observed in previous Phase II studies of genital warts and anal intraepithelial neoplasia.
- ◆ Key properties:
 - Curative in TC1 model of cervical cancer in mice
 - Induces Th1-biased cytokine profile and immune response *in vitro* and *in vivo*
 - Entire fusion construct is required for activity
- ◆ Although HspE7 is a construct based on the E7 protein from HPV type 16, preclinical and clinical data imply effective cross-reactivity with lesions of HPV types 6 and 11.

HspE7 Fusion Protein

- *M. bovis* BCG Hsp65
- Human Papillomavirus Type 16 E7



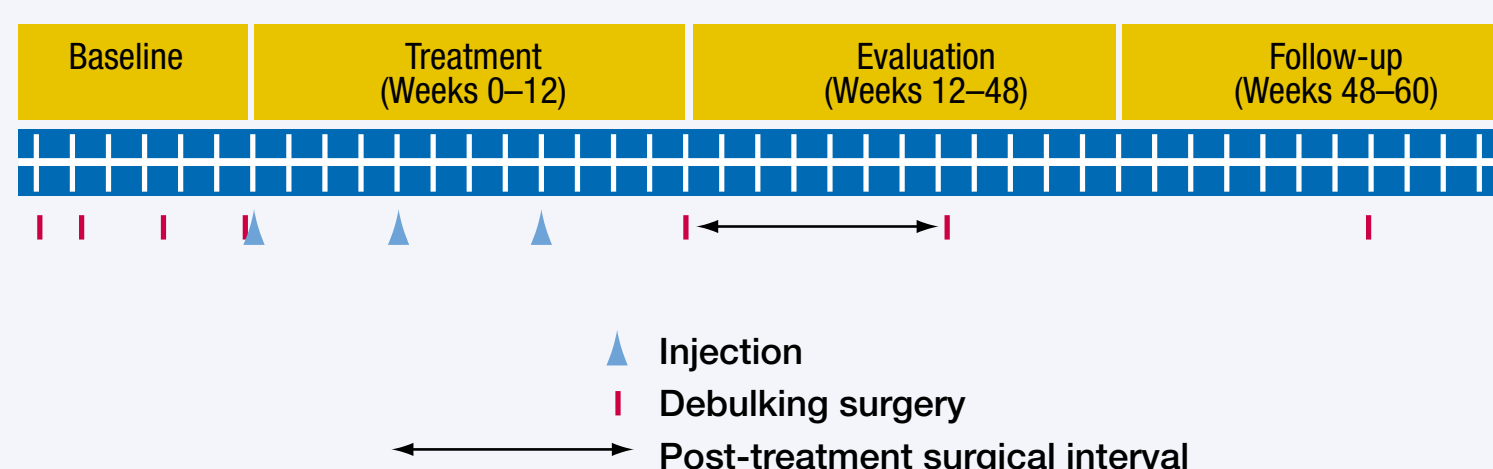
INTERVENTION STUDY 0005

Qualified subjects were enrolled following a clinically indicated surgical debulking procedure, marking Week -1. The initial subcutaneous injection of 500 mcg HspE7 was given within 7 days of the debulking procedure, marking Week 0, the beginning of the Treatment Period. The second and third injections of 500 mcg HspE7 were given monthly, at Weeks 4 and 8. The Evaluation Period began after Week 12 and continued through Week 48. The Follow-up Period began after Week 48 and continued through Week 60.

The first patient was enrolled 11/21/01. The last patient was enrolled 7/21/02 and will complete the study in 9/03. The data cutoff for this interim analysis was 3/21/03, chosen to permit an early efficacy read-out for all 27 patients. An update of this analysis with a data cutoff date of 6/27/03, when approximately 50% of patients completed the study, will be presented at the Society for Ear, Nose & Throat Advances in Children (SENTAC) annual meeting on 10/31/03.

Study Design

- Accrual goal of 27 patients with documented RRP
- Median pretreatment intersurgical interval determined using the four surgeries prior to treatment, which include the clinically indicated baseline debulking surgery
- Open label, 500 mcg HspE7 sc monthly x 3 over 60 days
- Follow-up continues to 60 weeks after initial debulking surgery



- RRP status was assessed by laryngoscopic and clinical measurement (Derkay/Cotrera Staging and Severity Scale)
- Laryngoscopic, clinical, and safety assessments made at regular intervals
- Additional surgical debulking performed as clinically indicated
- HPV typing obtained from biopsy specimens from debulking procedures at baseline and first post-treatment debulking surgery

Eligibility Factors

- Subject has had at least 4 debulking surgeries for RRP, including a debulking surgery occurring within 7 days of the first dose of HspE7
- No intersurgical intervals greater than 126 days during the period of the last 4 pretreatment surgeries
- No life-threatening or serious concomitant disorders other than RRP
- No disease or status that causes compromise of the immune system
- Free of concomitant medications that may suppress the immune system
- No history of ionizing radiation therapy to the respiratory tract
- No treatment with any investigational drug or other adjuvant RRP therapy (including interferon alpha, indole-3-carbinol, DHE photodynamic therapy, or cidofovir) within 30 days prior to Week 0
- No RRP treatment with specific or nonspecific immunotherapy (i.e., mumps vaccine injected intralesionally) within 9 months prior to Week 0
- Females of childbearing potential are neither pregnant nor lactating and are practicing an effective and appropriate method of birth control

Protocol-Defined End Points

Primary:

- Length of post-treatment intersurgical interval compared with median pretreatment intersurgical interval

Secondary:

- Change in RRP scale scores
- Change in annualized surgical rate
- Change in length of median intersurgical interval of all post-treatment surgeries
- Physician's, patient's, and guardian's global assessments

Results

Table 1. Study 0005 Population Baseline Characteristics

| | | Active N=27 |
|---|-----------|----------------|
| Gender | Male | 14 (52%) |
| | Female | 13 (48%) |
| Age (yrs) | Mean (SD) | 8.7 (4.46) |
| | Median | 8.0 |
| | Min-Max | 2-17 |
| | | |
| Weight (lbs) | Mean (SD) | 81.2 (42.9) |
| | Median | 63.0 |
| | Min-Max | 34-214 |
| | | |
| Race | Caucasian | 18 (66%) |
| | Black | 5 (19%) |
| | Asian | 1 (4%) |
| | Hispanic | 3 (11%) |
| | | |
| Pretreatment Intersurgical interval (days) | Mean (SD) | 55.3 (23.98) |
| | Median | 63.0 |
| | Min-Max | 14-101 |
| | | |
| Laryngeal scale score | Mean (SD) | 21.6 (12.69) |
| | Median | 20.0 |
| | Min-Max | 1-46 |
| | | |

Severe disease has been defined as a laryngeal scale score (anatomical component) ≥ 20 and/or the presence of pulmonary disease. This population was skewed toward severe disease with 13/27 patients (48%) meeting this definition. Moreover, the average number of surgeries per year at baseline in this population is higher than the estimated frequency of surgery in RRP patients according to the published literature.

Table 2. Analysis of Intersurgical Intervals, Including Subsets

| | Baseline median interval (days) | First post-treatment interval (days) | Median post-treatment interval* (days) |
|----------------------------|---------------------------------|--------------------------------------|--|
| All patients (N=27) | | | |
| Mean (SD) | 55.3 (23.98) | 95.6 (81.28) ^a | 83.1 (69.73) ^a |
| Median | 63.0 | 56.0 | 74.0 |
| Min-Max | 14-101 | 13-289 | 14-283 |
| Females (N=13) | | | |
| Mean (SD) | 54.4 (26.04) | 118.5 (88.49) ^a | 99.4 (72.23) ^a |
| Median | 42.0 | 110.0 | 83.0 |
| Min-Max | 21-101 | 29-289 | 28-283 |
| Males (N=14) | | | |
| Mean (SD) | 56.1 (22.86) | 74.4 (70.5) ^a | 68.0 (66.34) ^a |
| Median | 63.0 | 46.5 | 46.5 |
| Min-Max | 14-87 | 97.9 | 14-281 |

Change compared with baseline: ^a $p < 0.01$ ^b $p < 0.02$ ^c $p < 0.05$ ^d not significant

*Median intersurgical interval of all available intervals after each subject's Treatment Period. The date of last surgery is derived by assuming a surgery occurred the day after the End of Study. If the subject has not completed the study at interim analysis, the date of last surgery is derived by assuming a surgery occurred the day after the data cut-off date for interim analysis. Therefore, the post-treatment median intervals are underestimated in this analysis.

The increase in first post-treatment intersurgical interval is statistically significant ($p < 0.01$); likewise, the increase in the median of all post-treatment intervals is statistically significant ($p < 0.05$). For the overall population, the first post-treatment interval increased 79% over the pretreatment interval ($p < 0.02$). The effect in females appears to be more pronounced than in males. Some evidence, from this and other trials, suggests that males respond later than females to HspE7. These gender differences in response will be further defined in subsequent studies.

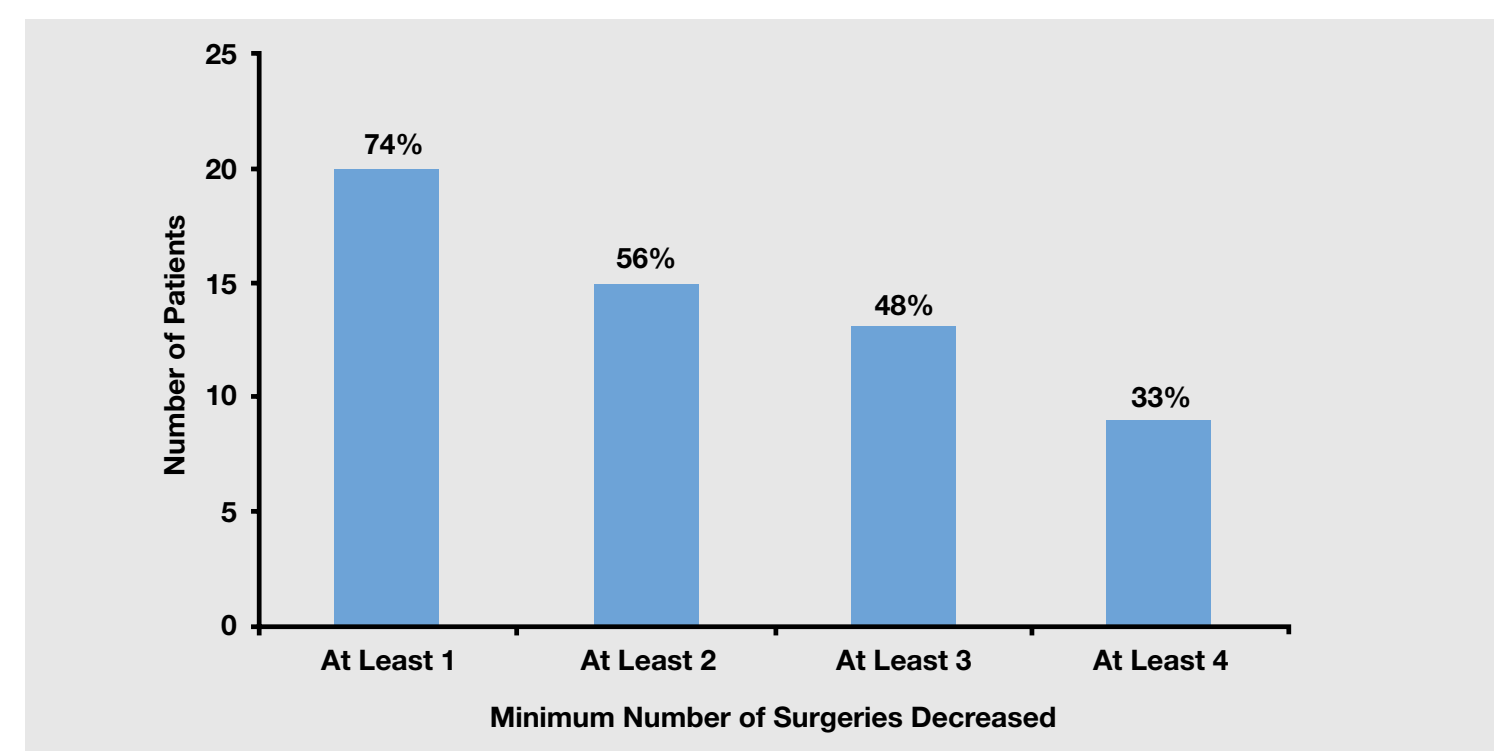
These results are based on interim data available as of March 21, 2003. The forward-looking statements in this document, including statements that project or anticipate an annualized reduction in surgeries for the patients, a sustained benefit of treatment and increased responses in males over time, remain subject to uncertainties. Additional data obtained through this trial or a clinical trial with a different design could lead to materially different results. See our most recent periodic securities filing for a discussion of uncertainties relating to clinical trials and other risks.

Table 3. Summary of Change in Annualized Surgical Rate

| | HspE7 500 mcg sc x 3 | p-value |
|------------------|----------------------|----------------|
| Pre-treatment | Mean (SD) | 8.68 (4.22) |
| | Median | 7.16 |
| | Min-Max | 4.6-25.1 |
| | | |
| Post-treatment | Mean (SD) | 5.88 (5.39) |
| | Median | 3.78 |
| | Min-Max | 0.0-26.1 |
| | | |
| Change in rate | Mean (SD) | -2.81 (2.30) |
| | Median | -2.85 |
| | Min-Max | -10.5-3.0 |
| | | |
| Percent decrease | Mean (SD) | -36.81 (39.02) |
| | Median | -36.95 |
| | Min-Max | -100.0-55.9 |
| | | |

The annualized surgical rate was calculated as the number of surgeries performed within a study period divided by the number of days in that period and multiplied by a factor of 365 days/year to estimate the number of surgeries per year. The reduction in the number of surgeries after treatment with HspE7 is highly statistically significant ($p < 0.0001$).

Figure 1. Number of Patients with a Decrease in the Annualized Surgical Rate Greater than or Equal to Various Thresholds



Within the population of patients who demonstrate a decreased annualized surgical rate displayed here, it may be projected that more than 50 surgeries could be avoided in the year after treatment.

Table 4. Proportion of Patients Who Doubled Their Post-treatment Intersurgical Interval

| | First post-treatment interval | Any post-treatment interval |
|----------------------------|-------------------------------|-----------------------------|
| All patients (N=27) | 8 (30%) | 11 (41%) |
| Females (N=13) | 6 (46%) | 8 (62%) |
| Males (N=14) | 2 (14%) | 3 (21%) |

The proportion of patients who doubled their pretreatment interval was examined because spontaneous doubling is unexpected in pediatric RRP. At this interim analysis, 41% of patients have improved by this rigorous criterion. Patients who have doubled intervals appear to have a sustained benefit since the median of all post-treatment intervals is statistically significantly increased, as shown in Table 2.

Conclusions

The internal consistency and strong statistical significance of data from Study 0005 suggest that HspE7 500 mcg sc x 3 is active in pediatric RRP.

This is the first report of efficacy in RRP with a therapeutic vaccine.

In Study 0005, the decrease in RRP patients' annualized surgical rates and absolute number of surgeries demonstrates the clinical benefit of treatment with HspE7.

A favorable safety profile was observed in Study 0005.

The results of Study 0005 warrant proceeding to Phase 3 studies with HspE7 in pediatric RRP.

Table 5. Details of Doubled-Interval Analysis*

| Patient number | Gender | Baseline median intersurgical interval (days) | First doubled intersurgical interval (days) | Increase from baseline |
|----------------|--------|---|---|------------------------|
| 102 | F | 63 | 189 | 200% |
| 103 | F | 42 | 122 | 191% |
| 104 | M | 63 | >281 | >346% |
| 302 | F | 42 | 110 | 162% |
| 303 | F | 30 | 61 | 103% |
| 401 | M | 39 | 120 | 208% |
| 501 | F | 33 | 74 | 124% |
| 503 | M | 63 | 140 | 122% |
| 805 | F | 101 | >283 | >180% |
| 903 | F | 36 | 289 | 703% |
| 904 | F | 66 | 133 | 102% |

*Shaded data highlights patients who doubled the first post-treatment interval

During follow-up to date, Patients 104 and 805 have had no post-treatment surgery. Although more females than males have responded to date, some males, such as Patients 104 and 401, have had outstanding responses.

Safety

Injection-Site Reactions

In general, HspE7 was well tolerated. As in previous studies, a high proportion of patients experienced injection-site reactions, generally transient and of mild to moderate severity. Injection-site reactions were recorded in patient diaries. They were not recorded as adverse events unless their severity or duration exceeded specified criteria.

Adverse Events Occurring in More Than 10 Percent of Study Population

| Preferred Term | HspE7 500 mcg sc x 3 N=27 (%) |
|-------------------------|-------------------------------|
| Any adverse event | 22 (81.5) |
| Any respiratory system* | 15 (55.6) |
| Fever | 8 (29.6) |
| Headache | 4 (14.8) |
| Infection | 4 (14.8) |
| Pain | 3 (11.1) |
| Nausea/vomiting | 3 (11.1) |

*Includes asthma, cough, dyspnea, pharyngitis, pneumonia, rhinitis, sinusitis

Discussion

- The primary measure of clinical benefit in Study 0005 was the number of surgeries performed post-treatment; patients experienced a statistically significant decrease in the number of post-treatment surgeries.
- Efficacy of treatment with HspE7, insofar as it reduces the number of surgeries required in the population as a whole, may be assumed to translate into significant reductions in morbidity to patients and significant savings in cost to patients' families and the national health-care system.
- In some patients, surgery has not been required after treatment with HspE7.
- The observation that the median of all post-treatment surgeries is statistically significantly increased ($p < 0.05$) suggests that the benefit of treatment is sustained beyond the first post-treatment intersurgical interval.
- Response data in Study 0005 is internally consistent in that response rate, mean duration of the first post-treatment intersurgical interval, median length of all post-treatment intervals, annualized surgical rate, and laryngoscopic scale scores were all consistent with clinical benefit.
- The finding of a higher response rate in female patients was unexpected, since gender differences in RRP prevalence or response have not been reported. Evidence from this trial and a genital warts trial, suggests that male patients may respond later than females to HspE7. Some male patients did have outstanding responses.