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MCRI Updates

Genocea Biosciences' (GNCA) Herpes Simplex Virus Vaccine Phase II Data Is Unimpressive

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Summary

We recently hosted a conference call to discuss Genocea Biosciences' (GNCA) GEN-003, a therapeutic vaccine to treat herpes simplex virus 2 (HSV-2) infections. The vaccine completed a phase II clinical trial and, as we expected, the results are horrible. There was absolutely no benefit on viral shedding one year after the last dose in any dosing group. Given the lack of effect in viral shedding we believe the "exploratory" endpoint of reduction in genital lesions by 42% is all artifact and the result of data mining. The company admits it needs to go back to the drawling board and perform a new phase II dosing study. There is no reason to believe a new dosing study will lead to positive data.

Stocks Impacted

- **Genocea Biosciences (GNCA-$18.75-NR)**

Background

- ***GEN-003 completed a phase II clinical trial for treating patients with recurrent herpes simplex virus 2 (HSV-2).*** Topline results of the phase II trial were presented today.

Reasons for Research

- ***Investors are attempting to determine if the results are positive.***

The Impact

- ***GNCA's goal of inducing a cytotoxic T cell response to cells infected with the herpes virus may not be a good thing.*** Such a response could lead to massive destruction of nerve cells infected with the virus. Through evolution, the immune system may have become unresponsive to cells infected with the herpes virus in order to spare the nervous tissue.
- ***There was no reduction in viral shedding at 12 months.*** This prospective endpoint was a complete failure. There was a non clinically significant 40% reduction of viral shedding at six months after the last dose, seen only with the 30 microgram dose. The lack of a dosing effect is consistent with artifact.
- ***Mean reduction in genital lesion rate is probably artifact related to data mining.*** GNCA reported a 42% percent reduction below baseline for the 30 microgram dose group. The company admits there was no dosing effect. A 42% reduction does not appear clinically significant and is unlikely to have an effect on transmission rates or symptoms. Given a complete lack of an effect on viral shedding, and no dosing effect, there is little biological plausibility for this result to be real.

MCRI Insights

- ***Based on the topline data as well as the reputed mechanism of action, we doubt this herpes simplex vaccine will be successful.*** The company admits it needs to go back to the drawling board and perform a new phase II dosing study. There is no reason to believe a new dosing study will lead to positive data.

Tech Assessment: Genocea Biosciences' (GNCA) Herpes Simplex Vaccine

I. GEN-003 for HSV-2 (Herpes Simplex Virus 2)
- Vaccine
- Therapeutic vaccine: Treat those with HSV-2 infection
- Reduce the duration and severity of clinical symptoms
- Protein subunit T cell-enabled
- ICP4: Immediate early protein
- gD2: Target of antibodies and T lymphocytes
- Matrix M2 adjuvant, from Novavax (NVAX-NR): Saponin derived

II. Proposed Mechanism of Action
- GNCA: Proprietary screening assay for vaccine antigens
- GNCA: Claims better able to identify antigens that induce a cytotoxic T cell responses
- Cytotoxic T cells are important for killing infected cells
- Our concern is that inducing cytotoxic T cell response could induce a demyelination disease, MS like

III. Herpes Simplex Virus Pathophysiology
- Two major types: HSV-1 and HSV-2
- HSV-1 originally associated with mouth infections in childhood
- HSV-1 increasingly being found in genital outbreaks
- HSV-2 originally associated with STD, genital herpes
- HSV-2 can be found outside the genital region

IV. HSV-2 Epidemiology
- HSV-2: 16% of people 14-49 in US infected, according to CDC
- African Americans: 39.2% infected
- Genital herpes is higher than 16% because of HSV-1
- CDC: Estimates based on antibodies in the blood
- Many antibody positive patients may not be symptomatic

V. HSV Diagnosis and Treatment

Diagnosis
- HSV cultures: Correlates with symptomatic herpes lesions
- Antibody titers: Correlates with prior herpes infections

Treatment
- Symptomatic treatment: OTC, keeping lesions clean, topical agents for pain
- Episodic treatment: Antiviral agents such as Valtrex, Zovirax, Famvir
- Suppressive treatment: Maintenance treatment with antiviral agents

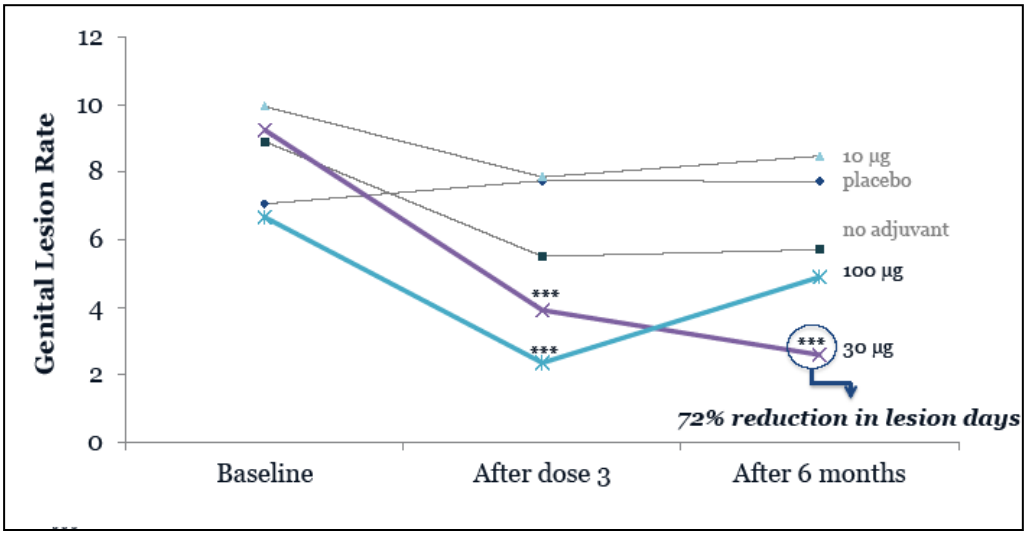
VI. Phase I/II Clinical Trial Design for GEN-003
- Double-blind, placebo-controlled
- Moderate to severe HSV-2 infections (three to nine outbreaks/year)
- Three separate doses at 21-day intervals
- N=143
- Five groups, 30 subjects in each
  - Placebo
  - Proteins only
  - GEN-003 (10 µg per protein + 50 µg adjuvant)
  - GEN-003 (30 µg per protein + 50 µg adjuvant)
  - GEN-003 (100 µg per protein + 50 µg adjuvant)
- Primary endpoint: Safety, tolerability by week 57
- Secondary endpoint: Immunogenicity (both humoral and cellular) at 33 weeks
- Secondary endpoint: Impact on viral shedding, proportion of days with viral shedding (six weeks)
- Impact on symptoms (exploratory)
- Interim results up to six months have been presented

VII. Phase I/II Interim Data on GEN-003

Figure 1. Viral Shedding, Primary Efficacy Result

Treatment Group	# of Subjects	(Post Dose 3) Mean Viral Shedding Frequency: Change from Baseline	p-value	# of Subjects	(After 6 Months) Mean Viral Shedding Frequency: Change from Baseline	p-value
Placebo	28	+11%	NS	23	+32%	<0.003
No adjuvant	28	+18%	NS	22	+14%	NS
GEN-003 (10 µg)	31	0%	NS	26	+54%	<0.001
GEN-003 (30 µg)	**29**	**-50%**	**<0.001**	**19**	**-40%**	**<0.001**
GEN-003 (100 µg)	27	-29%	<0.001	24	-18%	NS

Figure 2. Number of Clinical Lesion Days



Source: Company slides

VIII. Our Prediction

- GEN-003 will not be effective
- Interim results look like data mining
- Decreased viral shedding not clinically significant, even if it were real
- Long history of failure with HSV vaccines
- May be dangerous to immunize patients with HSV infections, demyelination

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