938

Safety, Tolerability, and Immunogenicity of GS-4774, an HBV-Specific Therapeutic Vaccine, in Healthy Volunteers

Anuj Gaggar,[1] Claire Coeshott,[2] David Apelian,[2] Tim Rodell,[2] Gong Shen,[1] Mani Subramanian,[1] John McHutchison[1]

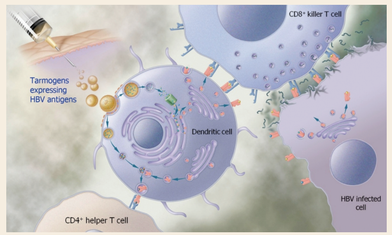
[1]Gilead Sciences, Inc., Foster City, CA; [2]GlobeImmune, Louisville, CO

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3252

Introduction

- ~350 million people are infected worldwide with hepatitis B virus (HBV)[1]
- Current treatments for chronic HBV adequately control viremia, but lead to loss of hepatitis B surface antigen (HBsAg) and anti-HBsAg seroconversion at low rates[2]
- A diminished T-cell response to HBV viral antigens is characteristic of chronic HBV infection[3-5]
- GS-4774 is a yeast-based vaccine expressing a recombinant protein aimed at eliciting an HBV-specific immune response[6]

Mechanism of Action



- Activates dendritic cells after phagocytosis
- Recombinant antigen epitopes are displayed via major histo-compatibility class I and II and stimulate CD4+ and CD8+ T cells
- Reduces levels of regulatory T cells

GS-4774 Structure

GS-4774 Recombinant Antigen

X = 60 amino acids
Large S = 399 amino acids
Core = 182 amino acids

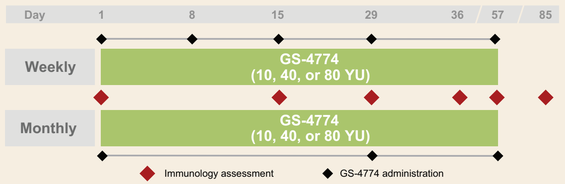
M = MADEAP metabolic stability tag
His_6 = 6 histidine-tag

Objective

- To assess the safety and immunogenicity of GS-4774 in healthy subjects

Methods

Study Design



- Single-center, open-label, dose-escalation study
- Healthy subjects without history of HBV vaccination received GS-4774 at 1 of 3 doses in 1 of 2 different dosing schedules
- **Primary endpoints:** safety and tolerability of GS-4774
- **Secondary endpoints:** immunogenicity of various doses and dosing regimens of GS-4774, as measured by:
  - Interferon (IFN)-γ enzyme-linked immunosorbent spot (ELISpot)
  - Lymphocyte proliferation assay (LPA)
  - Antibody responses to HBsAg, hepatitis B core antigen (HBcAg), and *Saccharomyces cerevisiae*
- Key inclusion criteria
  - Age ≥18 years
  - Negative scratch test for hypersensitivity to *S cerevisiae*
- Key exclusion criteria
  - History of HBV, hepatitis C virus, or HIV
  - History of HBV vaccination
  - History of autoimmune disease
  - History of positive serum HBsAg

ELISpot

- Peripheral blood mononuclear cells (PBMCs) were incubated *ex vivo* with 3 HBV recombinant antigens (HBsAg, HBcAg, and hepatitis B X antigen [HBx]), pools of overlapping 15-mer peptides representing target insert sequence of GS-4774, and pools of discrete peptide epitopes previously identified as cognate peptides for HBV-specific or GS-4774-specific T-cell responses
- Controls: medium alone, phytohemagglutinin (PHA), and pool of known CD8+ T-cell peptide epitopes
- IFN-γ+ cells/million PBMCs were enumerated and scores adjusted for background (medium alone) and baseline response
- Immune response was prespecified by algorithms that evaluated IFN-γ+ T-cell responses by breadth, duration, and magnitude

Lymphocyte Proliferation Assay (LPA)

- PBMCs were incubated *ex vivo* with HBsAg, HBcAg, and HBx for 6 days
- Proliferation was measured by uptake of ^{3}H-thymidine added for final 6 hours of incubation
- *Candida albicans,* tetanus toxoid, and PHA were used as positive controls
- Response: on-treatment response with stimulation index (SI) ≥2, where SI =

$$\frac{\text{median cpm of cells with antigen}}{\text{median cpm of cells with assay medium}}$$

Results

Demographics

	10 YU		40 YU		80 YU	
	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)
Mean age, y (IQR)	48 (39–55)	43 (33–47)	37 (35–40)	33 (26–40)	39 (30–44)	39 (33–45)
Men, n (%)	2 (20)	4 (40)	4 (40)	7 (70)	5 (50)	3 (30)
Race, n (%)						
White	9 (90)	10 (100)	10 (100)	10 (100)	8 (80)	9 (90)
Black	1 (10)	0	0	0	0	1 (10)
Native American	0	0	0	0	2 (20)	0
Hispanic/Latino, n (%)	5 (50)	6 (60)	8 (80)	8 (80)	7 (70)	8 (80)

IQR, interquartile range.

Adverse Events

	10 YU		40 YU		80 YU	
	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)
Patients with ≥1 AE, n (%)	7 (70)	4 (40)	9 (90)	6 (60)	7 (70)	6 (60)
Mild	5 (50)	4 (40)	8 (80)	5 (50)	6 (60)	5 (50)
Moderate	2 (20)	0	1 (10)	1 (10)	1 (10)	1 (10)
Patients with ≥1 serious AE, n (%)	0	0	0	0	0	0
No. of AEs	19	10	70	19	101	93
Mild, n (% total)	17 (89)	10 (100)	69 (99)	18 (95)	99 (98)	91 (98)
Moderate, n (% total)	2 (11)	0	1(1)	1 (5)	2 (2)	2 (2)
Severe, n (% total)	0	0	0	0	0	0

AE, adverse event.

Injection-Site Reactions

	10 YU		40 YU		80 YU	
	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)	Weekly (n=10)	Monthly (n=10)
Subjects with reactions, n (% total)	1 (10)	1 (10)	8 (80)	2 (20)	6 (60)	5 (50)
Injection-site reactions, n (% total AEs)	4 (21)	1 (10)	51 (73)	3 (16)	76 (77)	67 (74)
Mild, n (% reactions)	4 (100)	1 (100)	51 (100)	3 (100)	74 (97)	67 (100)
Moderate, n (% reactions)	0	0	0	0	2 (3)	0

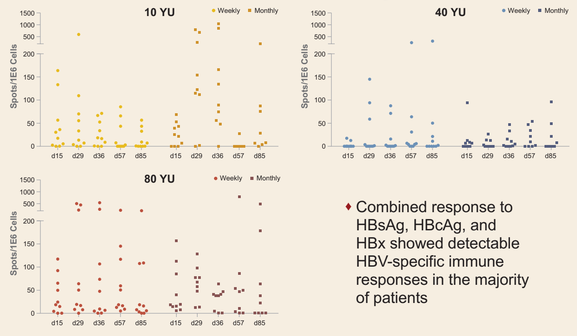
- The majority of injection-site reactions were mild
  - 2 moderate injection-site reactions (pain) in 1 subject in weekly 80-YU cohort
  - 2 mild injection-site reactions required therapy for relief (Tylenol [acetaminophen], ice)

Immunogenicity Summary

	10 YU		40 YU		80 YU	
n/N (%)	Weekly	Monthly	Weekly	Monthly	Weekly	Monthly
Any LPA response	6/8 (75)	4/5 (80)	9/9 (100)	9/9 (100)	9/9 (100)	8/10 (80)
Any ELISpot response	5/10 (50)	8/10 (80)	4/10 (40)	3/10 (30)	7/9 (78)	7/10 (70)

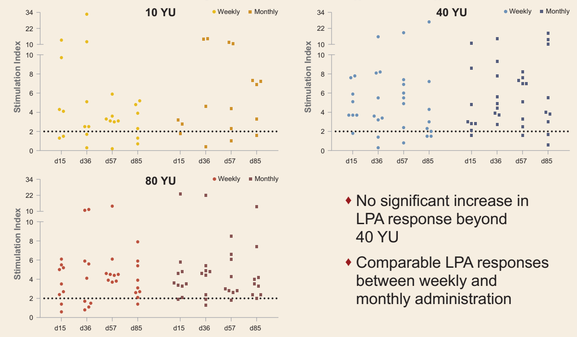
- All dose groups showed high levels of response by LPA
- No significant increase in ELISpot responses with weekly administration

ELISpot: Combined Response to HBsAg, HBcAg, and HBx



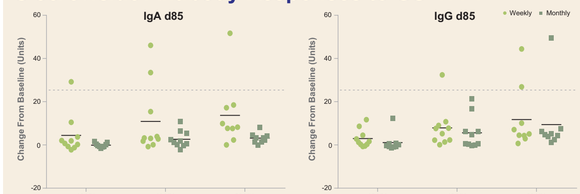
- Combined response to HBsAg, HBcAg, and HBx showed detectable HBV-specific immune responses in the majority of patients

LPA: Combined Response to HBsAg, HBcAg, and HBx



- No significant increase in LPA response beyond 40 YU
- Comparable LPA responses between weekly and monthly administration

S cerevisiae Antibody Responses to GS-4774



Dotted line denotes a positive response. Ig, immunoglobulin.

- No increases in hepatitis B surface or core antibody titers seen in any dose group during study

Human Leukocyte Antigen (HLA) Association With ELISpot Response

HLA Allele	Percent Subjects With Allele	Recombinant Antigen Response p-value*	Peptide Response p-value*
DQB1*03	60	1.0	.79
C*07	47	.80	.30
DRB1*04	45	1.0	.61
A*02	40	.80	.18
DQB1*05	33	.42	.78
DQB1*02	28	1.0	.14
DQB1*06	28	1.0	.25
C*03	28	1.0	.25
B*35	27	.77	1.0
A*24	27	1.0	.55
A*68	27	.56	.78
C*04	27	1.0	.78
B*39	27	1.0	1.0
DRB1*07	25	1.0	.015
DRB1*01	22	.36	.34

*p-value significance <0.001 based on Bonferroni correction for multiple hypothesis testing.

- No association of common HLA alleles with ELISpot response to peptides or recombinant antigens

Conclusions

- GS-4774
  - Was well-tolerated in healthy subjects
  - Elicited an immune response with monthly administration at all doses evaluated
  - Elicited an immune response to recombinant antigens and peptides
  - Immunogenicity was independent of host HLA alleles
- Further evaluation of GS-4774 in virally suppressed chronic HBV patients is ongoing

References

1. World Health Organization Hepatitis B Fact Sheet WHO/204, October 2000; **2.** Kwon H, et al. Nat Rev Gastroenterol Hepatol 2011;8:275-84; **3.** Bertoletti A, et al. J Gen Virol 2006;87:1439-49; **4.** Urbani S, et al. Hepatology 2005;41:826-31; **5.** Thimme R, et al. J Virol 2003;77:68-76; **6.** Stubbs AC, et al. Nature Med 2001;7:625-9.

Acknowledgments

This study was funded by Gilead Sciences, Inc.

Disclosures

A. Gaggar, G. Shen, M. Subramanian, and **J. McHutchison** are employees of and own stock in Gilead; **C. Coeshott** and **T. Rodell** are employees of GlobeImmune; **D Apelian:** no relevant financial relationship reported.

Presented at The Liver Meeting® 2013: 64th Annual Meeting of the American Association for the Study of Liver Diseases, November 1–5, 2013, Washington, DC