A novel PrimeBoost Immunotherapy induces high levels of HBeAg loss after 14 weeks in Patients with HBeAg^{+} Chronic Hepatitis B: A Phase IIa Clinical Trial

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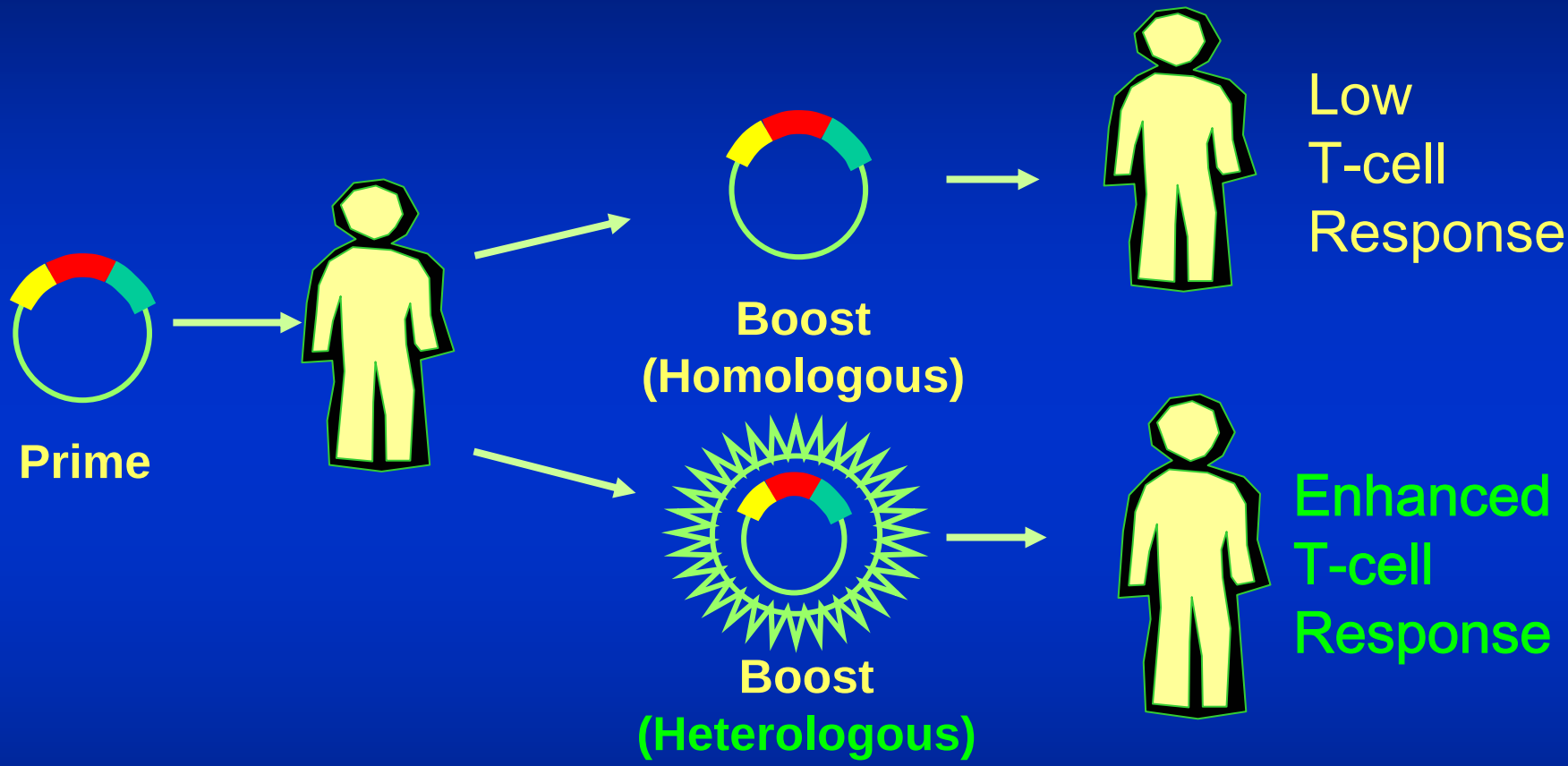
I have the following financial relationships to disclose:

I am an employee of Oxxon Therapeutics Inc. and my co-authors were clinical investigators in the study to be discussed. My presentation includes discussion of off-label and investigational use of medicines.

Introduction

- Heterologous PrimeBoost Immunotherapy
- Study Design
- Safety & Efficacy Data
- Cellular Immune Response
- Summary & Conclusions

Heterologous PrimeBoost



In this study:

Prime: 2 x DNA.HBs
Intramuscular injection
Week 0 & Week 3

Boost: 2 x MVA.HBs
Intradermal injection
Week 6 and Week 9

Study Design

A phase IIa study of a novel HBV therapeutic vaccine in HBeAg+ chronic hepatitis B patients

Two part study:

- Aim of Part 1 - to determine optimum dose of the vaccine
- Aim of Part 2 - to evaluate the efficacy of the vaccine alone, in combination lamivudine and vs. lamivudine alone

Part 1 (Dose Escalation Phase)

Primary Objective:

- To assess the tolerability and immunogenicity of 3 different dosing regimens:

Group	No. of Patients	DNA Prime	MVA Boost
Low Dose	7	2 x 1mg	2 x $5x10^7$ pfu
Mid Dose	6	2 x 2mg	2 x $1.5x10^8$ pfu
High Dose	6	2 x 2mg	2 x $5x10^8$ pfu

Part 2 (Efficacy Phase)

Primary Objective:

- To assess the anti-viral efficacy of the therapeutic vaccine:

Treatment Regimen	No. of Patients
Therapeutic vaccine alone	21
Therapeutic vaccine + lamivudine for 14 weeks*	22
Lamivudine for 14 weeks	11

*** 4 week run-in prior to immunisation**

Baseline Characteristics

Baseline parameter	Part 1			Part 2		
	Low Dose (n = 7)	Middle Dose (n = 6)	High Dose (n = 6)	Therapeutic vaccine (n = 21)	Therapeutic vaccine & lamivudine (n = 22)	Lamivudine (n = 11)
Mean ALT (IU/l)	101	106	74	97	101	106
Mean HBV DNA‡ (log_{10} copies/mL)	6.3	6.3	6.5	8.4	8.6	8.3

‡ Part 1: plasma HBV DNA assayed using COBAS AMPLICOR HBV MONITOR® Test (Roche Diagnostics); Part 2, COBAS TAQMAN 48 ANALYZER® (Roche Diagnostics)

Most Common Adverse Reactions

Adverse reaction	Part 1			Part 2			Total
	Low Dose (n=7)	Mid Dose (n=6)	High Dose (n=6)	Therapeutic vaccine (n=21)	Therapeutic vaccine plus lamivudine (n=22)	Lamivudine (n=11)	(n=73)
Injection site reaction	0	0	3 (50%)	9 (43%)	4 (18%)	0	16 (22%)
ALT /AST increase	1 (14%)	0	0	3 (14%)	1 (5%)	1 (9%)	6 (8%)
Pyrexia	0	0	2 (33%)	0	3 (14%)	0	5 (7%)

- n = number of patients in each group (and %)
- Adverse reactions with a total frequency of ≥5% shown

Summary of Serious Adverse Events

Serious Adverse Event	Part 1			Part 2			Total
	Low Dose (n=7)	Mid Dose (n=6)	High Dose (n=6)	Therapeutic vaccine (n=21)	Therapeutic vaccine plus lamivudine (n=22)	Lamivudine (n=11)	(n=73)
ALT/ AST increase	1 (14%)	0	0	2 (10%)	1 (5%)	1 (9%)	5 (7%)
Decomp. of diabetes	0	0	0	1 (5%)	0	0	1 (1%)
Total No. of SAEs	1 (14%)	0	0	3 (14%)	1 (5%)	1 (9%)	6 (8%)

Safety Summary

Heterologous PrimeBoost therapeutic vaccine well tolerated at all doses evaluated in chronic hepatitis HBeAg positive subjects

Seroconversion Rates

Time Point	Response	Part 1	Part 2			P value
		Therapeutic vaccine (n = 19)	Therapeutic vaccine (n = 21)	Therapeutic vaccine plus lamivudine (n = 22)	Lamivudine alone (n = 11)	
Week 14	HBeAg Loss	4 (21%)	5 (24%)	3 (14%)	1 (9%)	
	HBeAg Seroconversion	2 (11%)	3 (14%)	0	0	
Week 26	HBeAg Loss	Not Measured	6 (29%)	2 (9%)	0	
	HBeAg Seroconversion		3 (14%)	1 (5%)	0	
Week 52	HBeAg Loss	2 (11%)	Q106	Q106	Q106	
	HBeAg Seroconversion	1 (5%)				

Efficacy Summary (14 Weeks)

Response	Part 1 (Dose Escalation)	Part 2 (Efficacy Evaluation)		
	Therapeutic vaccine alone (n = 19)	Therapeutic vaccine alone (n = 21)	Therapeutic vaccine plus lamivudine (n = 22)	Lamivudine alone (n = 11)
Anti-viral Response				
HBeAg Loss	4 (21%)	5 (24%)	3 (14%)	1 (9%)
HBeAg Seroconversion	2 (11%)	3 (14%)	0	0
HBsAg Loss	0	0	0	1 (9%)
HBsAg Seroconversion	0	0	0	0
HBV DNA $<10^5$	2 (11%)	2 (10%)	9(41%)	6 (55%)
HBV DNA Change (mean log copies/ml)	-0.15	-0.54	-2.79	-2.86
Biochemical response				
ALT Normalisation	3 (16%)	1 (5%)	2 (9%)	1 (9%)

Cellular Immune Response

Sample Preparation

- PBMCs isolated (at a central lab) and cryopreserved within 6 hours
- Viability assessed after thawing
- Mean viability = 87%

Assays

- *Ex vivo* INFγ ELISPOT assay (overlapping HBs peptides and HBsAg) detects frequency of antigen-specific INFγ-secreting T cells

Ex vivo ELISPOT Responders (Peptides and HBsAg)

Response	Part 1 (Dose Escalation)	Part 2 (Efficacy Evaluation)		
	Therapeutic Vaccine alone	Therapeutic Vaccine alone	Therapeutic Vaccine plus lamivudine	Lamivudine alone
	(n = 19)	(n = 21)	(n = 22)	(n = 11)
Overlapping peptides	0 (0%)	6 (29%)	9 (43%)	5 (45%)
HBsAg	2 (11%)	3 (14%)	4 (18%)	1 (9%)

Higher magnitude responses were seen in the lamivudine groups (10-100 SFC per million) compared to the vaccine alone group (10-20 SFC per million)

Immune Response Summary

- Ex vivo INFγ ELISPOT detected only low level of HBs-specific T cell responses
  - Assays may not be sensitive enough
  - Peripheral blood compartment may not be not optimal
- Cultured ELISPOT assays ongoing

Efficacy Summary

- HBeAg clearance and seroconversion achieved in patients with HBeAg+ chronic Hep B at 14 weeks
- HBeAg response sustained at 26 weeks
- Associated HBV DNA suppression seen in seroconverters
- No additional increase in seroconversion rates with co-administration of lamivudine
- 52 week follow up ongoing

Conclusion

Heterologous PrimeBoost, a novel therapeutic vaccine strategy, offers the potential to be the first well tolerated immunotherapeutic treatment for chronic hepatitis B

Acknowledgements

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