Establishing functional cure of chronic HBV infection with nucleic acid polymers: Final results from the REP 401 study

M. Bazinet[1], V. Panteâ[2], G. Placinta[2], I. Moscalu[3], V. Cebotarescu[2], L. Cojuhari[2], P. Jimbei[4], L. Iarovoi[2], V. Smesnoi[4], T. Musteata[4], A. Jucov[2,3], A. Krawczyk[5,6], U. Dittmer[5], A. Vaillant[1]

1. Replicor Inc., Montreal, Canada
2. Nicolae Testemiţanu State University of Medicine and Pharmacy, Chișinău, Moldova
3. ARENSIA Exploratory Medicine Chișinău, Moldova
4. Toma Ciorbă Infectious Clinical Hospital, Chișinău, Moldova
5. Institute for Virology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
6. Department of Infectious Diseases, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

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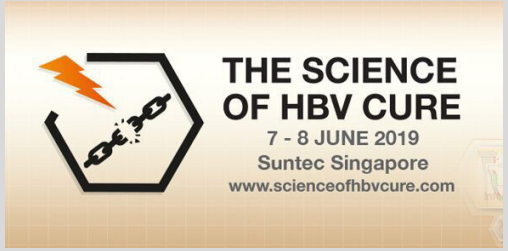


Breaking the chronicity of chronic HBV infection

Chronic HBV infection still persists in up to 350 million people. **WHY?**

HBsAg likely prevents the establishment of immune control:

HBsAg is the most abundant circulating viral antigen

- > 99.99% derived from subviral particles
  - Assembled and secreted independently from virions
  - Assembled and secreted in part independently of cccDNA (from integrated HBV DNA)
- **Cannot be targeted by direct acting antivirals**

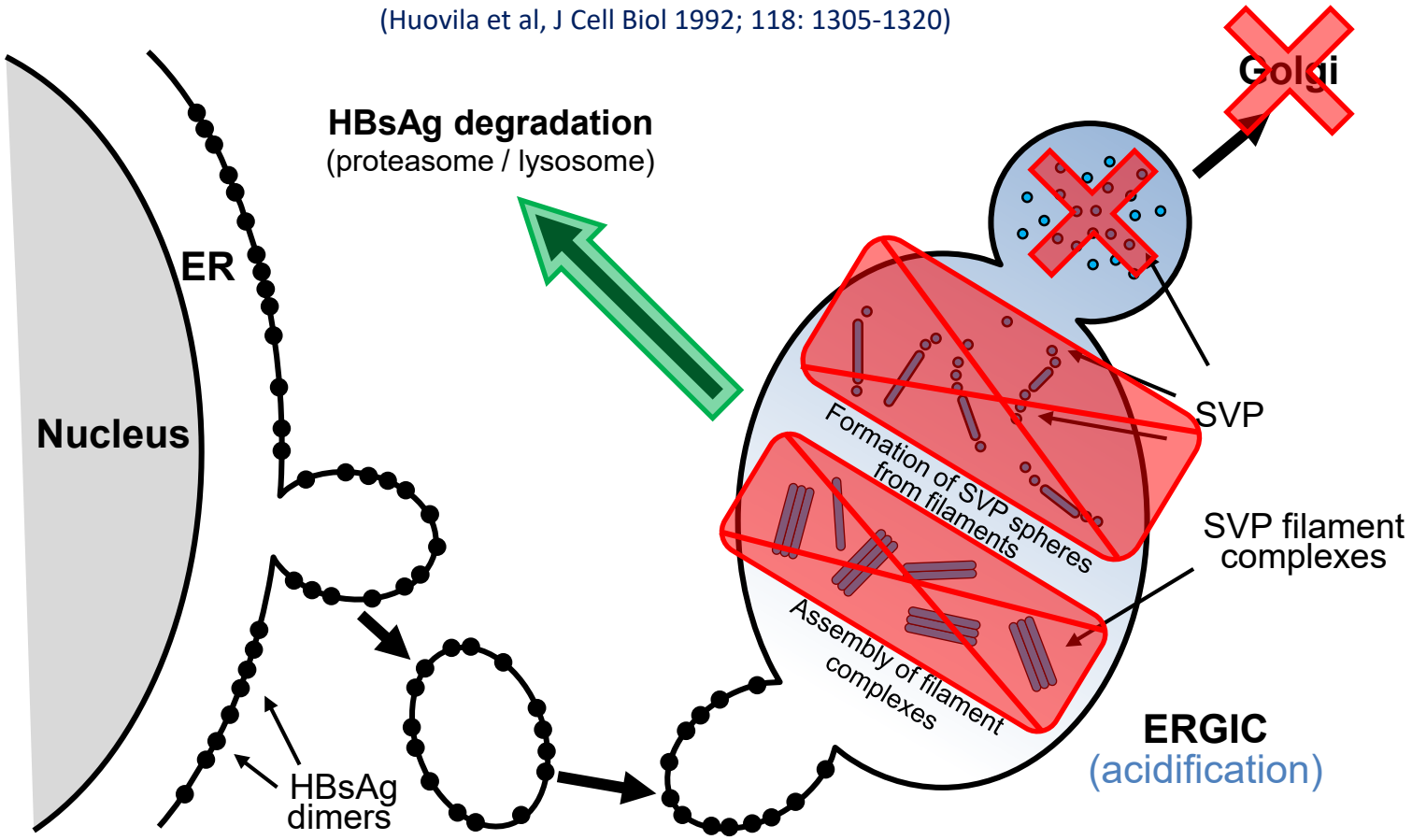
HBsAg is an important immune checkpoint inhibitor in chronic HBV infection

- Inhibits innate and adaptive immunity
- Exhausts the HBsAg specific B- and T-cell responses

Mechanism of action of REP 2139 in HBV

HBV subviral particle assembly pathway
(from cccDNA or integrated HBV DNA)

(Huovila et al, J Cell Biol 1992; 118: 1305-1320)



REP 2139 enters the ERGIC and inhibits SVP morphogenesis (host target currently unknown)

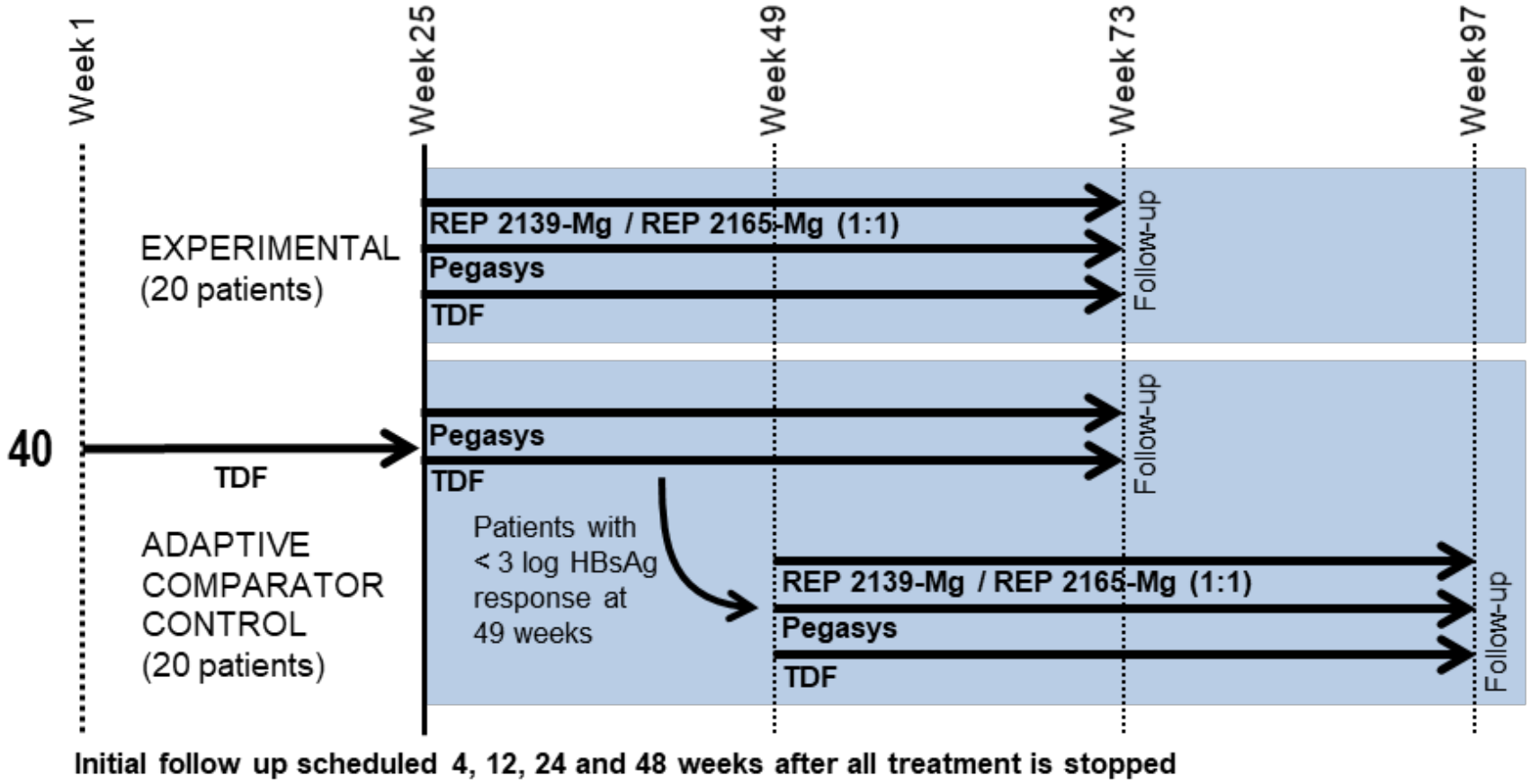
Intracellular degradation of HBsAg is enhanced

Inhibition of HBsAg secretion (from cccDNA or integrated HBV DNA) is accompanied by declines in intracellular HBsAg

Blanchet et al., Antiviral Res 2019; 164: 97-105

REP 401 Study

Clearing HBsAg to improve immunological recovery



TDF 300mg PO qD

Pegasys 180ug SC qW

NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW

REP 2165 = REP 2139 variant with improved tissue clearance

Roehl et al., Mol Ther Nuc Acids 2017; 8: 1-12

TDF + pegIFN + REP 2139-Mg or REP 2165-Mg

TDF: **Block production of infectious virus and replenishment of cccDNA**

Control of serum HBV DNA by TDF is unaffected by addition of pegIFN or NAPs

TDF + pegIFN: **Addition of immunotherapy to restore immune control**

HBsAg declines < 0.5 $\log_{10}$ from baseline in 17/20 patients after 24 weeks – further treatment futile

TDF + pegIFN + NAPs: **Lower intrahepatic HBsAg and block replenishment of serum HBsAg**

REP 2139-Mg = REP 2165-Mg over 48 weeks of triple combination therapy

Rapid HBsAg reduction (> 5 $\log_{10}$ reduction to 0.00 IU/mL [TND] as quickly as 10 weeks)

90% HBsAg response (> 1 $\log_{10}$ from baseline), 60% TND (within 24 weeks)

60% HBsAg seroconversion (up to 233,055 mIU/mL)

Transaminase flares (> 3X ULN) occurred in 95% of participants

Concomitant with HBsAg declines following addition of NAPs

Not accompanied by alteration in liver function or any signs of hepatic decompensation

(consistent with overall well tolerated and positive impact of transaminase flares in chronic HBV)

Final REP 401 outcome summary

(updated June 20, 2019)

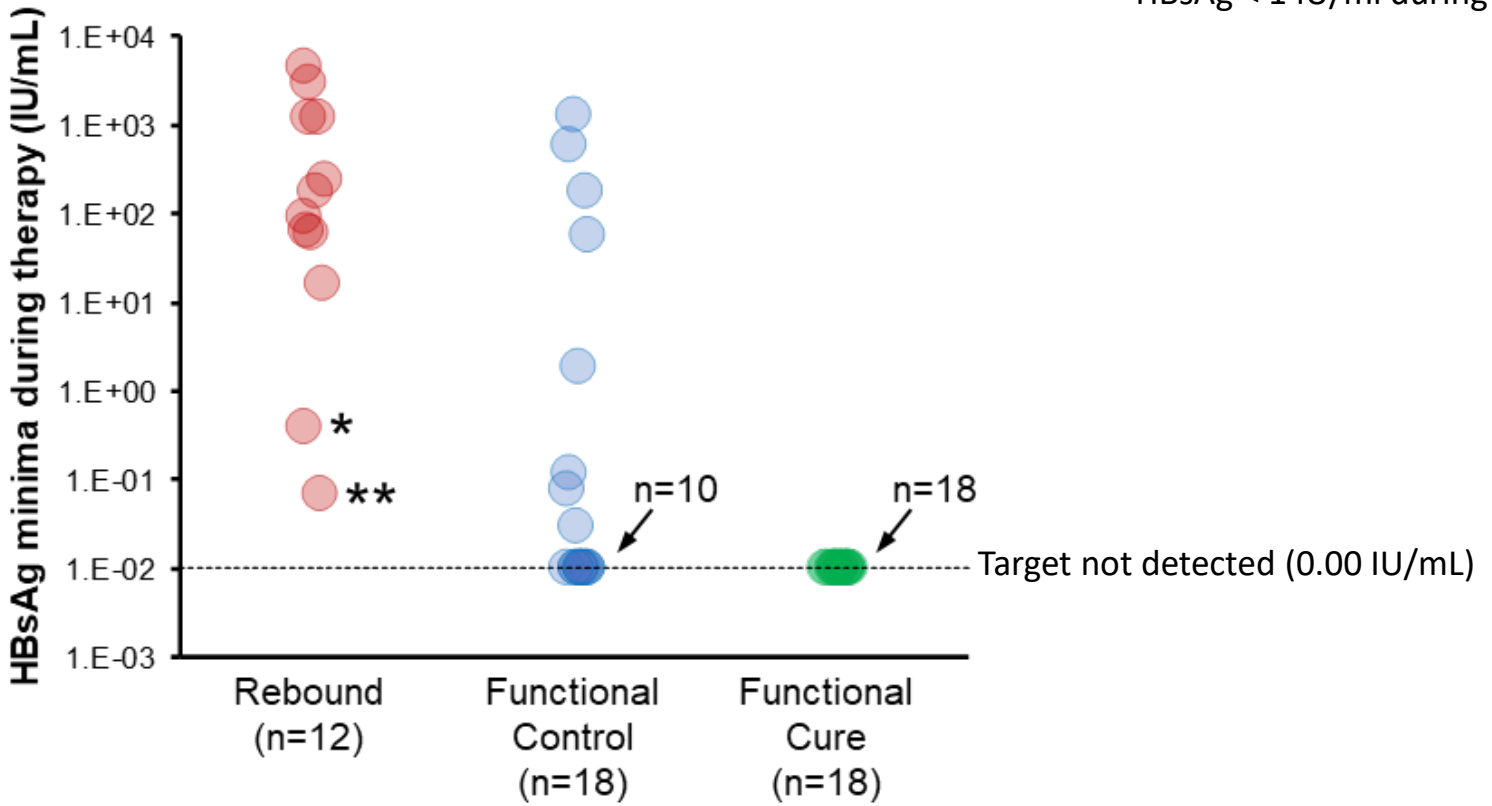
Completed treatment and ≥ 24 weeks of follow-up		36 (32 completed 48 weeks of follow-up)
Clinical response	Normal ALT	89%
	Normal liver median stiffness	56%
HBsAg response	< 1000 IU/mL	72%
	< 1 IU/ml	50%
	≤ LLOQ (0.05 IU/mL)	42%
	Seroconversion	53%
HBV DNA response	≤ 2000 IU/mL	78%
	Target not detected (TND)	47%
Virologic response	**Functional control (HBV DNA ≤ 2000 IU/mL, normal ALT)**	**39%**
	Functional cure (HBsAg < LLOQ, HBV DNA TND, normal ALT)	**39%**
	Clinical benefit, no therapy required (Low risk of progression, reduced risk of HCC)	**78%**

Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

* HBsAg < 1 IU/ml during last 4 weeks of therapy

** HBsAg < 1 IU/ml during last 20 weeks of therapy

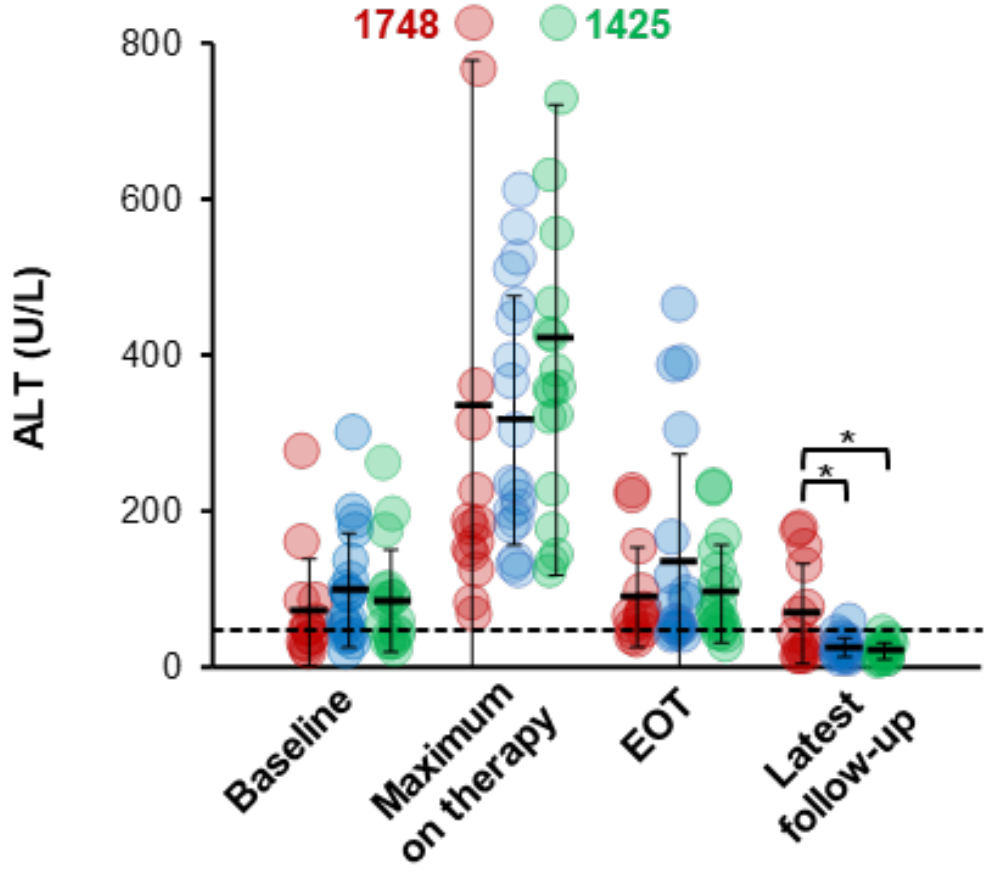


Achieving HBsAg 0.00 IU/mL during therapy is necessary but not sufficient to achieve functional cure

Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

ALT flares are prevalent during therapy leading to rebound, functional control or functional cure



Rebound

Functional control

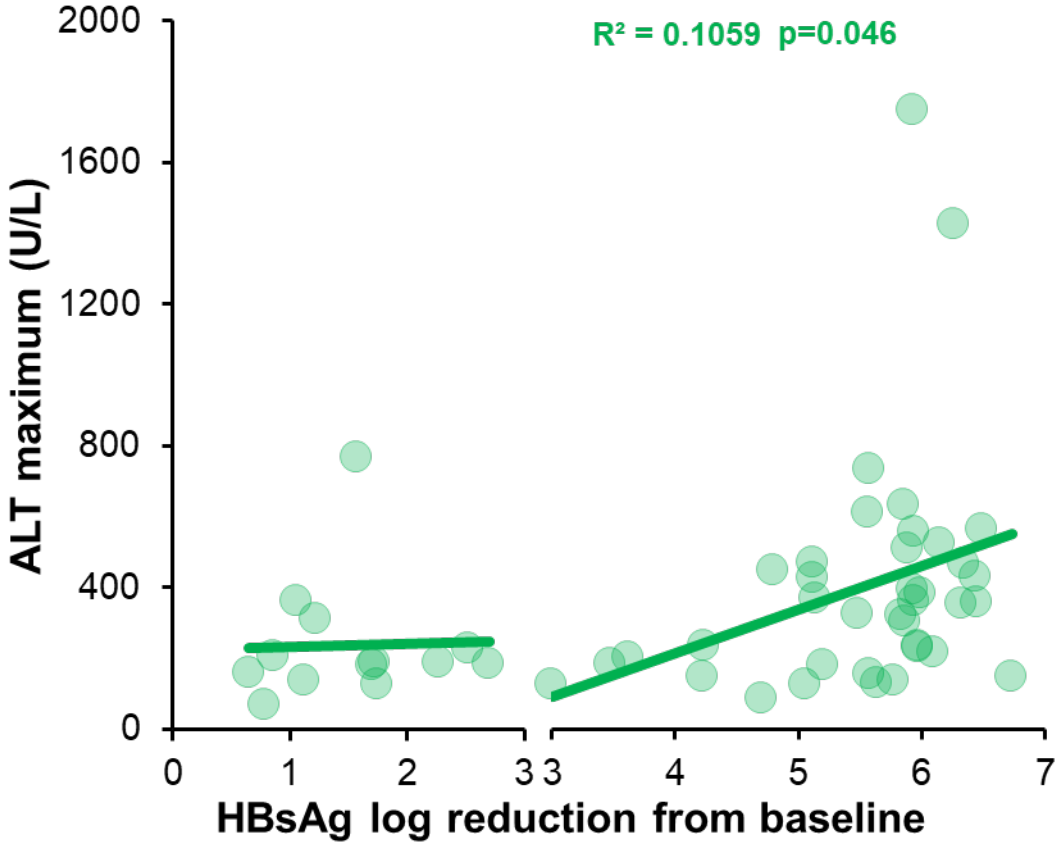
Functional cure

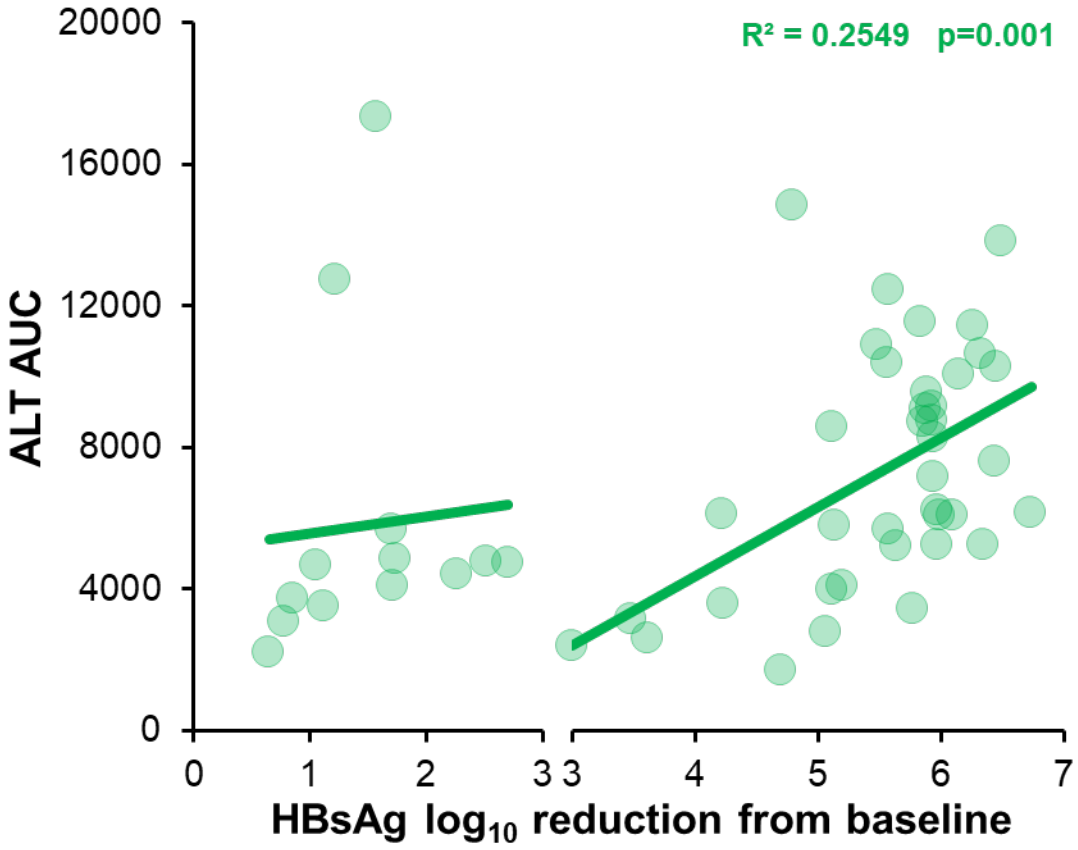
* Statistically significant with p< 0.05

Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

Increased ALT flare activity is correlated with HBsAg reductions ≥ 3 log_{10} from baseline

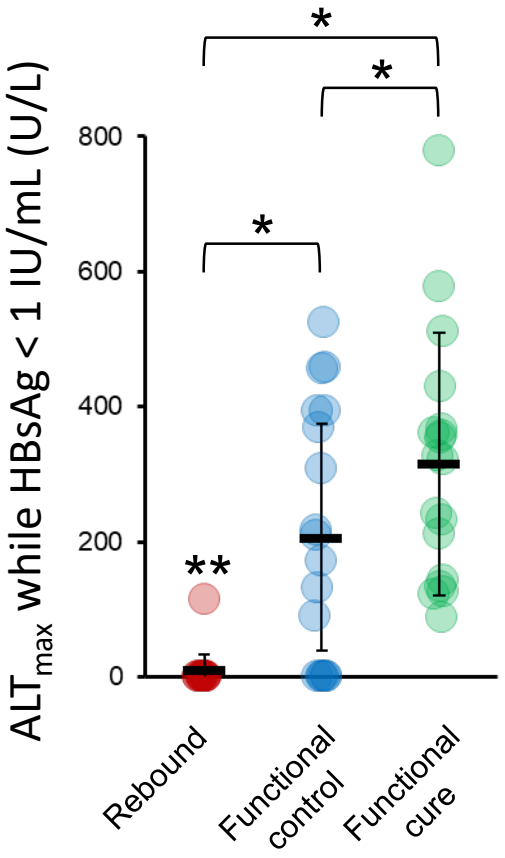


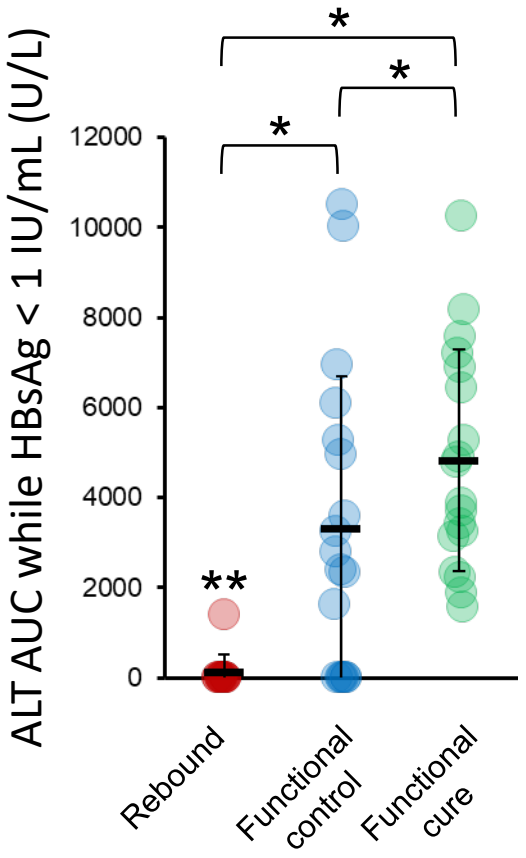


Predicting virologic outcomes

Meta analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

ALT flare activity while HBsAg < 1 IU/mL is correlated with virologic outcome





* Statistically significant with p< 0.05

** HBsAg < 1 IU/ml during last 20 weeks of therapy

Summary

Addition of NAPs to TDF + pegIFN dramatically improves outcomes off therapy

- Liver function normal in 91% of participants
- Reversal of inflammation / fibrosis
- Establishment of functional control / functional cure of chronic HBV infection in 83% of participants

Extent of ALT flare activity while HBsAg is < 1 IU/mL predicts outcomes after therapy

- No flare activity with HBsAg < 1 IU/mL = rebound
- Increased flare activity while HBsAg is < 1 IU/mL is correlated with better likelihood of achieving functional cure
- Restoration of HBsAg specific immune function during therapy (T-cell mediated?) may drive establishment of clinical benefit persisting after therapy

REP 2139-Mg transition to SC with TDF + pegIFN is expected to further improve HBsAg response and have similar or better outcomes against HBV / HDV co-infection (to be assessed in upcoming REP 501 trial).

IV Phase IIA US study (A5382) will confirm optimal REP 2139-Mg dose to allow early entry into a phase IIB pivotal study with SC administration.

A collaborative effort !

Clinical evaluations:

Montreal, Canada
Michel Bazinet

Dhaka, Bangladesh
Mamun Al-Mahtab

Chișinău, Moldova
Victor Pântea
Valentin Cebotarescu
Lilia Cojuhari
Pavlina Jimbei
Gheorghe Placinta
Liviu Iarovoi
Valentina Smesnoi
Tatiana Musteata
Iurie Moscalu
Alina Jucov

US (ACTG)
Marion Peters
Shyam Kottilil
Claudia Kawkins

Clinical virology and assay validation:

Essen, Germany
Adalbert Krawczyk

Munich, Germany
Michael Roggendorf
Hadi Karimzadeh
Hrvoje Mijočević
Zainab Usman

Los Angeles, USA
Peter Schmid
Jeffrey Albrecht

Bobigny, France
Emmanuel Gordien
Frédéric Le Gal

Abbott
Gavin Cloherty

Pre-clinical evaluations:

Adelaide, Australia
Allison Jilbert
Faseeha Noordeen
Catherine Scougall

Lyon, France
Lucyna Cova
Celia Brikh
Jonathan Quinet
Catherine Jamard

Essen, Germany
Michael Roggendorf
Katrin Schöneweis
Mengji Lu
Pia Roppert
Dieter Glebe

Logan, Utah, USA
John Morrey
Neil Motter

Reno, Nevada, USA
Doug Kornbrust

Mechanistic studies:

Montreal, Canada
Matthieu Blanchet
Patrick Labonté
Richard Boulon
Léna Angelo

Paris, France
Camille Sureau
Frauke Beilstein
Matthieu Lemasson

Essen, Germany
Ruth Broering
Catherine Real
Joerg Schlaak

Ness Ziona, Israel
Raphael Mayer
Merav Merom Shamur
Ronny Peri-Naor