# Clinical Validation of an Orally Delivered, Systemically Activated TLR7 Agonist to Boost Host Immune Response to Chronic Viral Diseases, Including Hepatitis B Virus

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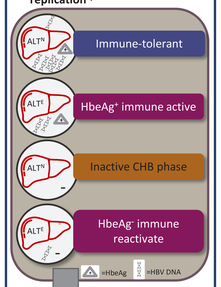
## Background

**1**

**Chronic Hepatitis B (CHB) is a multiphase infection with a dynamic relationship between host immune response and viral replication[1,2]**

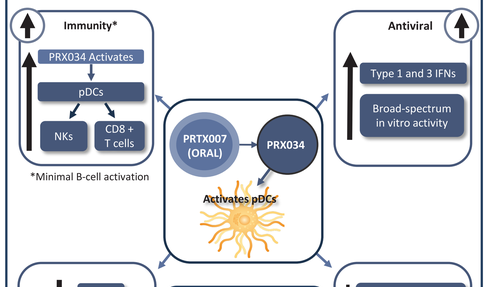



**Optimal Treatment Goal[1,2]**
Functional cure; rarely achieved
Combinatorial CHB therapy offers a potential pathway to a functional cure

For more information see Terrault NA, Bzowej NH, Chang K-M, et al. 2016[1] and Lim SG, Baumert TF, Boni C, et al. 2023[2]

**2**

**PRTX007 is an oral prodrug that systemically delivers the nucleoside-based, toll-like receptor 7 (TLR7) agonist, PRX034. PRX034 avoids NFκβ-mediated inflammation while stimulating beneficial immune responses via pDCs in preclinical models and healthy volunteers[3-8]**




For more information see Appleman JA, Webber S, Zook S, et al 2022[3] and Lemech CR, Argent C, Scribner CL, et al. 2023[5]

**Pharmacodynamic Biomarker Response and Relative Sensitivity to Optimized TLR7 Agonists**

↑ TLR7 mRNA > ↑ ISG mRNAs > ↑ Cytokine/Chemokine/Other Plasma Factors > ↑ IFN

## Objectives and Phase 1 Design Rationale

**Primary**
- Assess clinical safety and tolerability of PRTX007 in healthy volunteers

**Secondary**
- Assess the pharmacokinetic characteristics of both PRTX007 and PRX034
- Compare the pharmacokinetic profiles of free-base and salt forms of PRTX007
- Assess the pharmacodynamic responses of PRX034 over single and multiple doses in normal healthy volunteers

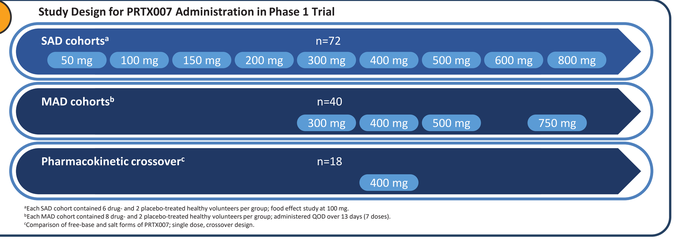
**Rationale for conducting a phase 1 study in healthy volunteers**
- Identify drug-specific adverse events (AEs) and pharmacodynamic markers, which is not possible to do in combination therapy in patients with chronic viral infections
- Increase clinical sampling, allowing investigators to build a comprehensive pharmacodynamic profile
- Identify specific active dosing range for use in infectious viral disease studies, significantly reducing time, costs, and patient burden in future studies

## Methods

- This was a first-in-human, phase 1, single-center, prospective, randomized, double-blind, placebo-controlled study of 9 single-ascending dose (SAD) cohorts and 4 multiple-ascending dose (MAD) cohorts of PRTX007 **administered orally every other day (QOD)** to adult healthy volunteers in Sydney, Australia[4]
  - The 500-mg MAD cohort terminated early (after fifth dose) because of a temporary COVID-related facility closure
- Safety data were collected throughout the study; pharmacokinetic and pharmacodynamic data were collected at predetermined intervals pre- and post-dose

**3**

**Study Design for PRTX007 Administration in Phase 1 Trial**



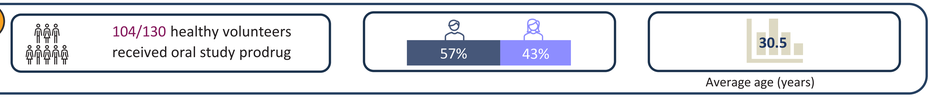

[a]Each SAD cohort contained 6 drug- and 2 placebo-treated healthy volunteers per group; food effect study at 100 mg.
[b]Each MAD cohort contained 8 drug- and 2 placebo-treated healthy volunteers per group; administered QOD over 13 days (7 doses).
[c]Comparison of free-base and salt forms of PRTX007; single dose, crossover design.

## Results

### Participant Characteristics

**Clinical Studies**

**4**




### Safety

*See also Table 1*

- 110 total AEs recorded
- 42 AEs attributed to PRTX007
- Headache was the most common treatment-related AE

- There were no Grade 3 or higher AEs
- There were no clinically meaningful changes observed in creatinine, BUN, or uric acid
- There was no dose modification or discontinuation due to treatment-related AEs

**5**

**Table 1. Most common AEs coded as treatment-related compared with placebo**

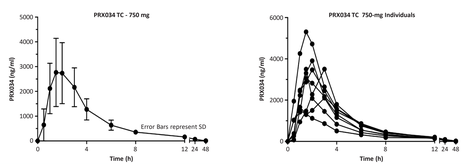
| AEs (X from N=130) | Placebo (n=26) | PRTX007 (n=104) | PRTX007 Percent (X/104=%) Grade Response | | |
|---|---|---|---|---|---|
| | | | Grade 1 | Grade 2 | Grade 3 |
| **Nervous System Disorders** | | | | | |
| Headache (40)[a] | 4 | 17[b] | 12% | 5% | 0% |
| **Hepatobiliary Disorders** | | | | | |
| Elevated ALT (5)[b] | 0 | 5[b] | 5%[c] | 0% | 0% |
| **General Disorders** | | | | | |
| Fever (transient) (4) | 1 | 3[d] | 3% | 0% | 0% |

[a]Nineteen additional headaches in the PRTX007-treated group were coded as unrelated to drug. There was no dose dependence.
[b]No significant changes in aspartate transferase, bilirubin, or alkaline phosphatase were observed.
[c]Four of 5 HVs exhibited levels between 1.5x and 2x the upper limits of normal (ULN); 1 HV was at ~2.8x the ULN.
[d]Transient fever; resolved within 24-36 hours and did not recur upon subsequent dosing.

### Pharmacokinetics

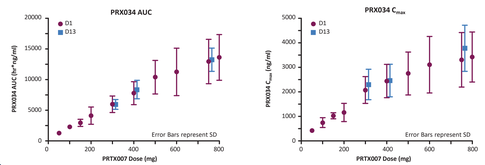
**6a**

**Time Course (TC): Short Duration of Pulsatile Systemic Exposure to PRX034 on Day 1 (750-mg PRTX007 Cohort, n=8)**




**6b**

**Dose Level: Dose-Proportional Increase in Exposure to Active Agonist; Exposure Unchanged Between First (D1) and Seventh (D13) Doses**

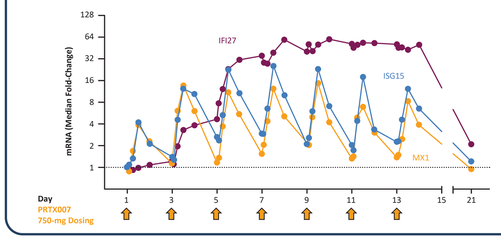



### Pharmacodynamics

**7**

*See also panel 11*

**Repeated QOD Doses of PRTX007 Increase the Magnitude of mRNA Response (750-mg PRTX007 Cohort, n=8)**




**8**

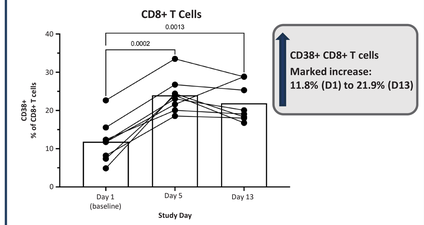
*See also panel 11*

**The well-controlled, coordinated immune response observed after a single dose is maintained during repeated doses**

**Two healthy volunteers who were poorly responsive to first dose (first dose response highlighted in red box) established a robust response upon repeated dosing**

**9**

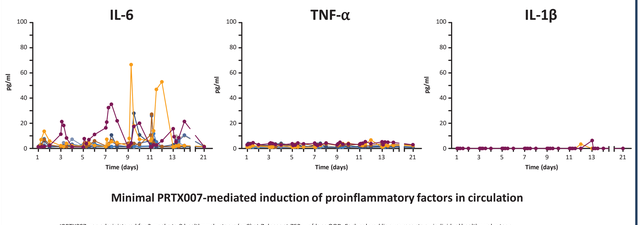
**Activation of CD8+ T cells by PRTX007 QOD Dosing (750-mg PRTX007 Cohort, n=8)[a]**




[a]PRTX007 was administered for 2 weeks to 8 healthy volunteers (n=8) at 7 doses at 750 mg/dose QOD.

**10**

**Individual Time Course of Proinflammatory Cytokine Profiles (750-mg PRTX007 MAD Cohort, n=8)[a,b]**



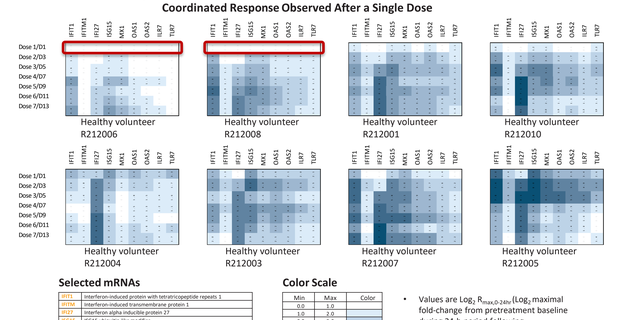

**Minimal PRTX007-mediated induction of proinflammatory factors in circulation**

[a]PRTX007 was administered for 2 weeks to 8 healthy volunteers (n=8) at 7 doses at 750 mg/dose QOD. Each colored line represents an individual healthy volunteer.
[b]Day 1 was the predose data point and serves as a baseline. Day 21 was 8 days post-last dose and shows cytokine levels return to baseline.

### Pharmacodynamics (cont.)

**11**

**mRNA Transcript Induction Heat Maps for the 750-mg Multiple-Dose Cohort Maintain the Coordinated Response Observed After a Single Dose**




**Selected mRNAs**

| | |
|---|---|
| IFIT1 | Interferon-induced protein with tetratricopeptide repeats 1 |
| IFITM | Interferon-induced transmembrane protein 1 |
| IFI27 | Interferon alpha inducible protein 27 |
| ISG15 | ISG15 ubiquitin-like modifier |
| MX1 | MX dynamin-like GTPase 1 |
| OAS1 | 2′-5′-oligoadenylate synthetase 1 |
| OAS2 | 2′-5′-oligoadenylate synthetase 2 |
| IRF7 | Interferon regulatory factor 7 |
| TLR7 | Toll-like receptor 7 |

**Color Scale**

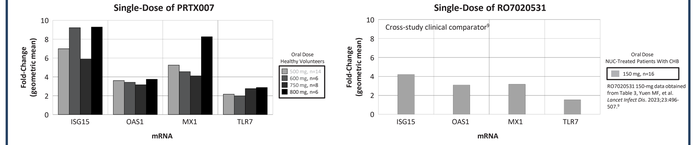
| Min | Max | Color |
|---|---|---|
| 0.0 | 1.0 | |
| 1.0 | 2.0 | |
| 2.0 | 3.0 | |
| 3.0 | 4.0 | |
| 4.0 | 5.0 | |
| 5.0 | 6.0 | |
| 6.0 | 7.0 | |
| 7.0 | 10.5 | |

- Values are $Log_2$ $R_{Day1/D-24hr}$ ($Log_2$ maximal fold-change from pretreatment baseline during 24-h period following administration of PRTX007) for each subject in the MAD cohort.

### Cross-Study Clinical Comparator

**12**

**mRNA Fold-Change Following Single Doses of PRTX007 vs RO7020531***




RO7020531 150-mg data obtained from Table 3, Yuen MF, et al. *Lancet Infect Dis.* 2023;23:496-507.

**After administration of oral prodrug, both TLR7 agonists stimulate transcription of antiviral mRNAs**

*Maximal response within 36 hours of dosing on Day 1.

## Conclusions and Discussion

- PRTX007 demonstrated a favorable safety profile when administered in healthy volunteers in phase 1 studies
  - AEs were mostly mild; no SAEs observed
- Repeated oral QOD doses of PRTX007 increased the magnitude of antiviral mRNA response
  - The short half-life of the drug allowed a targeted short pulse of exposure to active agonist without accumulation of drug between doses
- PRTX007 activated innate and adaptive immune responses, including important effector cell populations, without systemic increases in proinflammatory factors
  - PRTX007 administration induced ISGs without significantly increasing circulating IFNs
  - No increase in expression or circulating levels of proinflammatory cytokines was observed
  - CD8+ T-cell activation (CD38+ markers) increased markedly from pretreatment to end of dosing in all healthy volunteers
  - PRTX007 also activates CD8+ NK cells[8]
- Both the clinical characteristics and unique pattern of immune induction by PRTX007 support its use in combinatorial therapy for a functional cure of CHB infection
  - Functional cure with improved clinical outcomes is the current, optimal goal in CHB therapy, but this is rarely achieved with currently available agents[1,2]
  - Like PRTX007, R07020531 is an orally administered prodrug that systemically delivers a novel, nucleoside-based TLR7 agonist[9]
  - R07020531 is in clinical development to establish a functional cure for patients with HBV; it is currently in a phase 2 study investigating its use as part of a combinatorial therapy for treatment of CHB infection[9]
- Consistent with its anti-inflammatory properties and intentionally designed short half-life, the results of this phase 1 study support the safety and tolerability of PRTX007 treatment in patients with chronic viral diseases, including CHB

### References

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### Disclosures and Acknowledgements

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**Abbreviations**: AE=adverse events; Ag=antigen; $ALT^{N}$=normal alanine aminotransferase levels; $ALT^{E}$=elevated alanine aminotransferase levels; AUC=area under the curve; BUN=blood urea nitrogen; $C_{max}$=maximum serum concentration; CHB=chronic hepatitis B; D=day; h=hours; HbeAg=hepatitis B e antigen; HBV=hepatitis B virus; h=hour; IFN=interferon; IL-1=interleukin 1; IL-6=interleukin 6; ISG=interferon-stimulated gene; MAD=multiple-ascending dose; MOA=mechanism of action; mRNA=messenger RNA; NFκβ=nuclear factor kappa β; NK=natural killer cell; NUC=nucleoside or nucleotide analogue; pDC=plasmacytoid dendritic cell; QOD=every other day dosing; TC=cytotoxic T cell; TH1=T helper type 1; TLR7=toll-like receptor 7; TME=tumor and its surrounding microenvironment; SAD=single-ascending dose; SAE=serious adverse event; SD=standard deviation; TNF-α=tumor necrosis factor alpha.