IMC-I109V, a novel soluble T cell receptor (TCR) bispecific (ENVxCD3) designed to eliminate HBV-infected hepatocytes in chronic HBV patients: initial data from a first-in-human study

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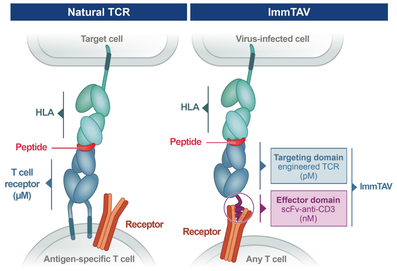
Abstract # 3331

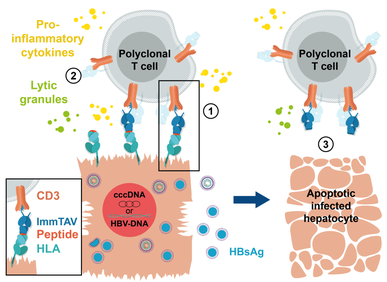
Background

- HBsAg clearance is the treatment goal for chronic hepatitis B (CHB). However, HBsAg loss occurs infrequently with standard of care therapies and investigational direct-acting antivirals, even with long treatment durations[1].
- Persistence of transcriptionally active HBV DNA, whether integrated or extrachromosomal (cccDNA), drives chronic HBsAg production; new strategies that enable safe elimination of hepatocytes harbouring HBV genomes are needed[2].
- Immune-mobilising monoclonal TCR against viruses (ImmTAV®) are unique bispecific soluble proteins designed to redirect polyclonal T cells, regardless of their specificity, to eliminate virus-infected cells[3].
- IMC-I109V is an affinity-enhanced HBV-specific TCR fused to an anti-CD3 scFv T cell activating moiety (ImmTAX™) that redirects non-exhausted effector T cells to eliminate hepatocytes presenting HLA-bound HBsAg (Env)-derived peptide[4].

Mechanism of action of ImmTAV molecules



IMC-I109V redirects any non-exhausted effector T cell to kill HBV-infected hepatocytes



Mechanism of action of IMC-I109V (ENVxCD3)

1. IMC-I109V engages pHLA on HBV-infected hepatocyte and CD3 on passing T cell
2. Activated T cell releases pro-inflammatory cytokines and lytic molecules
3. Activated T cell triggers apoptosis of infected hepatocyte

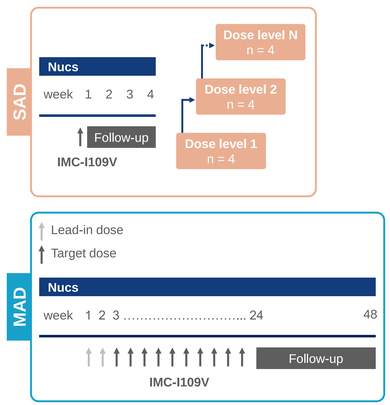
PD biomarkers (transient):
↓ Absolute lymphocyte count
↑ IL-6, CXCL10, IFN-γ etc
↑ ALT

Viral biomarkers:
↓ HBsAg
↓ HBcrAg
↓ HBV RNA

Methods

- IMC-I109V-101 is an open-label Phase 1/2 study evaluating IMC-I109V in HLA-A*02:01 positive patients with HBeAg-negative CHB who are non-cirrhotic, and virally suppressed on nucleos(t)ide analogues.
- Since the IMC-I109V mechanism of action results in hepatocyte lysis and T cell cytokine release, transient liver enzyme elevations and systemic cytokine-related events are expected. This first-in-human study therefore incorporates several measures to mitigate the risk of severe liver flares and cytokine release syndrome.
  - Part 1 is a single ascending dose (**SAD**) to identify safe and pharmacologically active doses
    - *Starting dose based on the minimum anticipated biological effect level (MABEL)*
  - Part 2 is a multiple ascending dose (MAD) to evaluate safety and anti-HBV activity of repeated doses over 24 weeks
    - *Target dose(s) to be based on pharmacologically active doses identified in Part 1*
    - *Intrapatient dose escalation to reach the target dose*
- All participants receive premedication with anti-pyretics and anti-histamines
- Secondary objectives include pharmacokinetic (PK) profile and effects on serum HBsAg, HBcrAg and HBV RNA levels.

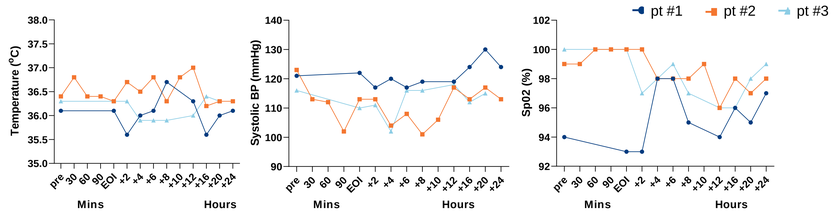
Study design



Results

- Through pre-screening, 21 patients have been identified as HLA-A*02:01-positive to date. Of these, 14 proceeded to screening.

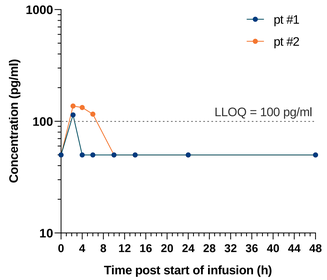
Figure 1. IMC-I109V dosing at MABEL (0.8 mcg) was well tolerated and was not associated with cytokine release syndrome



IMC-I109V was administered by IV infusion over 2 hours. Vital signs were monitored before, during and after treatment. EOI = end of infusion. SpO2 values for pt #1 from pre-infusion to 2 hours post EOI were not considered clinically significant.

- Three patients have each received a single dose of 0.8 mcg, based on MABEL
- Doses were well tolerated and not associated with adverse events in any subject

Figure 2. Preliminary PK analysis: maximum serum concentration is consistent with the dose level



Concentrations less than the lower limit of quantitation (LLOQ) of the assay (100 pg/mL, as shown by dashed line) were plotted at half of LLOQ for illustrative purposes only. Note pt #3 data not shown as was not available at time of data cut-off.

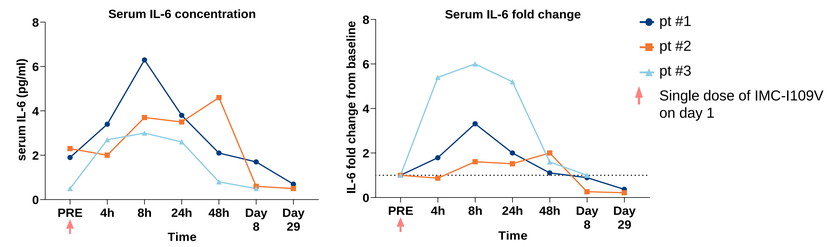
Table 1. PK parameters

	T_{max}* (h)	C_{max} (pg/ml)	T_{last}* (h)	AUC_{last} (h*pg/ml)
Participant 1	2.02	114	2.02	115
Participant 2	2.02	137	6.0	654
Mean (n=2)	2.02	126	4.01	385
SD	0	16.3	2.82	381

* Time from start of infusion

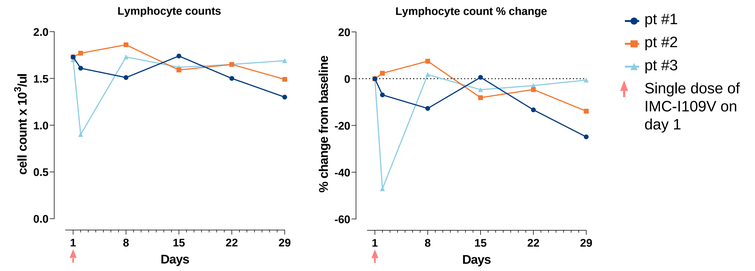
- Individual PK profiles following IV infusion of 0.8 mcg IMC-I109V over 2 hours were available for the first two participants
- By 12 hours, serum concentrations had declined below the lower limit of quantification

Figure 3. IMC-I109V induces transient upregulation of serum interleukin-6 in 3/3 patients following a single 0.8 mcg dose



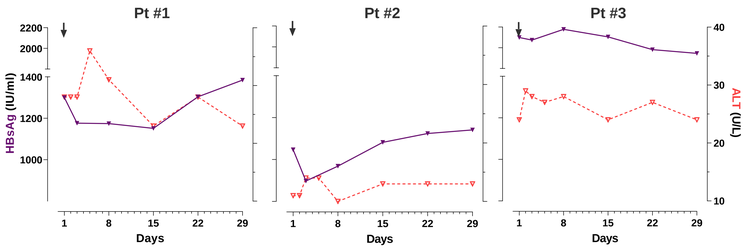
- IMC-I109V induced transient elevation in serum interleukin-6 (IL-6) post infusion, consistent with MoA
- Higher IL-6 fold changes post treatment correlated with higher baseline HBsAg, also consistent with MoA

Figure 4. Lymphocyte margination observed in 1/3 participants post single dose of IMC-I109V (0.8 mcg)



- Transient lymphocyte margination is expected based on the IMC-I109V MoA
- 1/3 patients showed 47% reduction in lymphocyte counts 24 hours post infusion with IMC-I109V

Figure 5. Trends and kinetics of HBsAg and ALT changes observed post single dose of IMC-I109V (0.8 mcg) are consistent with the MoA



Arrow indicates timing of administration of IMC-I109V

- Serum HBsAg levels transiently decreased by 11-15% during Days 3-15 post infusion, before returning to baseline within 3 weeks
- The decreases coincided with small, transient elevations in ALT, albeit within the normal range

Conclusions

- Administration of a single dose of IMC-I109V based on the MABEL was not associated with cytokine release syndrome or any other adverse event
- The concomitant HBsAg declines and elevations in ALT and IL-6 indicate that a single, very low dose of IMC-I109V elicited on-target activity consistent with the TCR bispecific (ENVxCD3) mechanism of action, without adverse events
- These preliminary data are encouraging for the prospect of identifying a tolerable and active treatment regimen with higher and repeat dosing
- Enrolment in Part 1 dose escalation continues to evaluate this novel mechanism designed to eliminate HBV-positive hepatocytes. (Eudract no. 2019-004212-64)

References

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