Comparison of Different Allometric Scaling Approaches to Project Human PK of CD388, a Novel Drug-Fc Conjugate, in Development for Influenza Prevention

Poster 5298

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BACKGROUND

CD388 is a novel drug-Fc conjugate (DFC) comprising a novel neuraminidase inhibitor stably linked to a human IgG1 mutant Fc fragment engineered for plasma half-life extension by enhancing binding to the human neonatal Fc receptors (FcRn) at low pH. CD388 is being developed for the universal prevention of influenza and nonclinical studies have demonstrated efficacy against a large panel of seasonal and pandemic influenza A and B strains in both lethal and nonlethal mouse models of infection.

A reliable projection of human pharmacokinetics (PK) characteristics, especially plasma half-life, allows for the design of an optimal first-in-human (FIH) clinical study with adequate safety monitoring and plasma sampling intervals. As CD388 represents the first DFC advanced into clinical development, it was important to understand the optimal preclinical-to-clinical scaling approach.

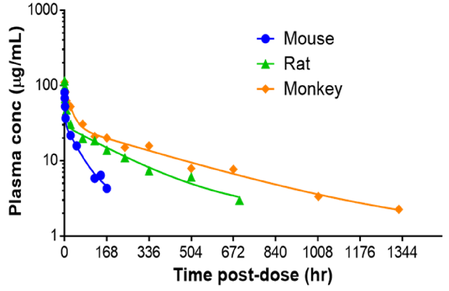
METHODS

Single-dose PK were studied in mouse, rat, and monkey. Plasma clearance (CL) from IV-PK of different species combinations were regressed against mean animal bodyweight to derive allometric exponents for CL. The allometric exponent of 0.85 for CL as reported by Deng, et al.[1] for therapeutic monoclonal antibodies was also compared. Monkey-to-human PK scaling by the species-invariant time method, i.e., Dedrick [2] was then used to project human PK profiles to estimate plasma half-life ($t_{1/2}$). Phoenix WinNonlin was used to fit the human PK profiles to a 2-compartment model. The mean human plasma $t_{1/2}$ of ~48 ~days observed in the CD388 first-in-human Ph1 study [3] in healthy subjects was used for comparison to predicted human plasma $t_{1/2}$.

RESULTS

The PK profile of CD388 was investigated in the mouse, rat, and cynomolgus monkey by intravenous (IV; mouse, rat, monkey, **Figure 1**), and by intramuscular or subcutaneous (IM or SC; mouse) dosing. CD388 consistently exhibited a relatively low CL and long half-life across all species tested, ranging from approximately 4.4 (mouse) to 15 (monkey) days. The time to reach Cmax from either IM or SC dosing was typically 24 hours suggesting effective absorption via these dose routes.

Figure 1: Inter-species comparative PK profiles of CD388 at 5 mg/kg IV.



Plasma CL from mouse and/or rat plus monkey were regressed against animal bodyweights to derive an allometric exponent for clearance based on different combinations in **Table 1**.

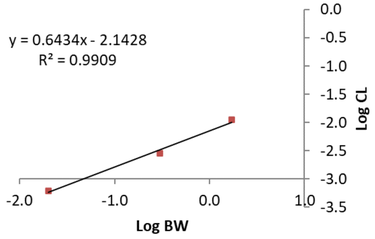
Table 1: Standard allometric exponent for CL based on different rodent and monkey combinations.

Species	Allometric Exponent (β)
Mouse, Rat, Monkey	0.64
Mouse, Monkey	0.65
Rat, Monkey	0.79
Deng et al. [1]	0.85

RESULTS

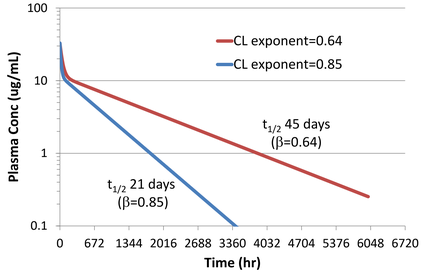
Figure 2 shows the allometry regression/equation from all 3 species.

Figure 2: Standard allometry for CL using mouse, rat, and monkey CL.



Using the Dedrick approach, human PK profiles (**Figure 3**) were projected from monkey data using allometric exponents for clearance ranging from 0.64 to 0.85, while using a fixed exponent of 1.0 for volume of distribution. Following monkey-to-human conversion, the projected human PK profile was then fitted to an IV 2-compartment model. The resulting $t_{1/2}$ from each projection ranged from 21 to 45 days and were subsequently compared to the actual human $t_{1/2}$. The highest $t_{1/2}$ of this range, 45 days (using CL exponent 0.64 from 3 species allometry) was closest to the observed human $t_{1/2}$ of ~48 days.

Figure 3: Human PK (2 mg/kg) profiles predicted from monkey PK using the lowest and highest allometric exponents.



DISCUSSION/CONCLUSION

Although not as large as a typical human IgG1 antibody of ~150 kDa, the molecular weight of CD388 (~65 kDa) is still considerably larger than a typical small molecule therapeutic (<1 kDa). However, scaling using exponents typical of small molecule therapeutics provided a better prediction of human CD388 PK, especially $t_{1/2}$.

This information will be useful to optimize human PK predictions as Cidara continues to pursue its Cloudbreak™ platform of novel DFCs.

With regards to CD388 use as an influenza prophylaxis, the actual $t_{1/2}$ of ~48 days was long, which could potentially allow for once per flu season dose administration.

REFERENCES

1. Deng, et al. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data. What have we learned? mAbs 3:1, 61-66; 2011
2. Dedrick. Animal scale-up. J Pharmacokinet Biopharm. 1:435-61; 1973
3. Flanagan, et al. Single Ascending Dose Safety, Tolerability, and Pharmacokinetics of Subcutaneous and Intramuscular CD388, a Novel Long-acting Drug-Fc Conjugate for Universal Prevention of Seasonal and Pandemic Influenza [Poster 2514] presented at IDWeek; Oct 2023; Boston, MA.

DISCLOSURE

All authors are shareholders & employees of Cidara Therapeutics.

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