Mechanistic Evaluation of Efficacy Using Biomarkers of the Oral, Small Molecule, Factor D Inhibitor, Danicopan (ACH-4471), in Untreated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)  

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BACKGROUND  

In PNH, a somatic mutation in the PIGA gene of one or more hematopoietic stem cells generates a clone of abnormal erythrocytes which lack two key alternative pathway (AP) regulatory proteins, CD95 and C95B, leading to uncontrolled complement activation on affected erythrocytes (RBCs) and membrane attack complex (MAC)-mediated lysis.1  

Factor D (FD), a serine protease, catalyzes the cleavage of complement factor B into Ba and Bb, which allows for the formation of the AP C3 convertase. By inhibiting FD, danicopan, an oral small molecule FD inhibitor, blocks C3 convertase formation, the control point for AP activation as well as the amplification of all complement pathways. This leads to inhibition of C3 cleavage, C3 fragment deposition, terminal pathway activation and MAC formation. Therefore, FD is a promising target in diseases of excess activation of the AP, such as PNH.  

OBJECTIVES  

Correlation between complement activity biomarkers and clinical/laboratory efficacy of danicopan, administered as monotherapy, in the treatment of PNH. Given that danicopan is a potential first in class AP inhibitor for the treatment of PNH, it is important to investigate changes and relationships among relevant biomarkers of the AP to better understand the mechanism of action of danicopan in vivo.  

METHODS  

Danicopan starting doses ranged from 100-150 mg PO QBH, with dose escalation up to 200 mg QBH based on response. Plasma concentrations were determined by liquid chromatography/tandem mass spectrometry (LC/MS-MS). Pharmacodynamics (PD) were determined by measuring serum AP activity (AP; Wieslab). Plasma Bb concentration, serum FD concentration, serum complement C3 concentration, and serum classical pathway (CP) activity were also measured. C3 fragment deposition on RBCs was measured by flow cytometry with FITC conjugated anti-human C3d antibody.  

RESULTS  

Clinical results were previously presented,1 Table 1.  

Table 1.  

| Day of Trial | Day 1 | Day 6 | Day 13 | Day 20 | N=10 | N=10 | N=10 | N=10 | N=8 | N=8 | N=8 | N=8 |
|-------------|------|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Baseline    |      |      |      |      | 0.5 | 1.0 | 1.5 | 2.0 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| Clinical Pathways |      |      |      |      | 0.5 | 1.0 | 1.5 | 2.0 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| % Cells (%) |      |      |      |      | 0.5 | 1.0 | 1.5 | 2.0 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
| SUA/mL      | 1.8 | 2.6 | 3.2 | 2.5 | 1.8 | 2.6 | 3.2 | 2.5 | 1.8 | 2.6 | 3.2 | 2.5 | 1.8 |
| Hct (g/dL)  | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 |
| Total Bilirubin (mg/dL) | 1.31 | 1.03 | 1.03 | 1.03 | 1.31 | 1.03 | 1.03 | 1.03 | 1.31 | 1.03 | 1.03 | 1.03 | 1.31 |
| MAC Factor D (ng/mL) | 32 | 44 | 56 | 44 | 32 | 44 | 56 | 44 | 32 | 44 | 56 | 44 | 32 |

In addition to ex vivo serum AP activity, plasma Bb concentration, an in vivo biomarker for FD inhibition, was assessed (Figure 3). At baseline, higher than normal Bb levels were observed, demonstrating ongoing activation in vivo AP activity. Following danicopan dosing, Bb levels decreased into normal range, demonstrating decreased in vivo C3 convertase formation. There is a strong, positive correlation between Bb concentration and LDH levels (Table 2), demonstrating Bb as a reliable biomarker of AP activation in vivo during therapeutic complement inhibition. A strong negative correlation was observed between Bb concentration and danicopan inhibition (Table 2) validating the role of danicopan in the changes of these endpoints.  

As expected, serum FD concentration was unchanged throughout treatment (Figure 4A). The slight increase in serum C3 concentration is likely due to blockade of constitutive C3 consumption which may be elevated in PNH due to impaired control of complement activation on the RBC surface (Figure 4B). Furthermore, CP activity was not inhibited as expected (Figure 4C), further demonstrating that danicopan is a specific AP inhibitor.  

Lastly, in contrast with C5 inhibition, C3 fragment deposition on erythrocytes was very low (<0.5% of erythrocytes) throughout treatment (Figure 5) despite a significant increase in the clone size of PNH erythrocytes.  

CONCLUSIONS  

This previously reported, proof of concept study with oral danicopan, administered as monotherapy, demonstrated that upstream complement inhibition at the level of FD can prevent MAC-mediated intravascular hemolysis, even in the absence of terminal pathway blockade (i.e., C5 inhibitor). Notably, improvements in multiple clinical endpoints occurred with danicopan monotherapy where optimal AP inhibition was not achieved throughout the dosing period. The correlation analysis among danicopan concentration, AP activity, Bb concentration, LDH level and C3 fragment deposition demonstrated that meaningful inhibition of AP activity leads to sustained control of intravascular hemolysis, without emergence of C3-mediated extravascular hemolysis. A second-generation, oral FD inhibitor is under development possessing higher potency and improved PK profile, allowing for twice daily dosing with a mean value of >95% inhibition of AP at steady state.  

REFERENCES  


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