PP.102

DNTH103 shows sustainable inhibition of complement and prevents nerve conduction velocity impairment in a preclinical model of CIDP

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BACKGROUND

C1s is a novel, development-stage target for complement-mediated nerve damage in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The complement system plays a role in the development of CIDP[1]

- A loss of function mutation in the CD59 gene (that protects from membrane attack complex (MAC) -mediated injury) is associated with demyelination via MAC activation and plays a vital role in the demyelination seen in early-onset CIDP[2,3]
- A study showed that CIDP patients had significantly higher mean serum and cerebrospinal fluid (CSF) levels of C5a and terminal complement components than healthy control patients[4]
- Two separate studies have demonstrated deposition of C3 and C3d complement components in sural biopsies from patients with CIDP[5,6,7]
- Passive transfer of immunoglobulin G (IgG) antibodies from CIDP patient sera induced a demyelinating phenotype in the rodent model of experimental autoimmune neuritis, with C3 deposition at the affected site[5]

C1s is a key component of the classical complement pathway[8]

- Active C1s protein is the C1 complex serine protease responsible for activating the downstream classical complement pathway[7]
- C1s only triggers the classical complement pathway, and not the lectin or alternative complement pathways[8]

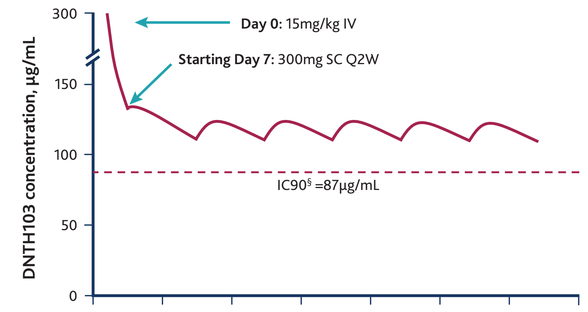
C1s inhibitors are novel therapeutic candidates in CIDP[1]

- Humanized anti-C1s monoclonal antibody riliprubart* showed positive results in a Phase 2 proof-of-concept study in 43 patients with CIDP[9]

DNTH103 is a picomolar-potent monoclonal antibody selectively targeting active C1s

- DNTH103 is an investigational fully human IgG4 monoclonal antibody with picomolar potency engineered to selectively bind to only the active form of C1s, allowing for a low-volume formulation suitable for SC self-administration
- Alternative and lectin pathways are left intact, potentially resulting in a reduced risk of encapsulated bacterial infection
- DNTH103 includes the YTE† half-life extension technology resulting in a 60-day half-life, which is expected to enable potent inhibition of the classical pathway with infrequent dosing

Global Phase 2 studies in generalized Myasthenia Gravis (gMG) and Multifocal Motor Neuropathy (MMN) are ongoing, and a global Phase 2 trial in CIDP is planned to start in 2024



Simulation using data from 60 healthy volunteers dosed across multiple cohorts demonstrates potent inhibition with infrequent SC dosing

*Riliprubart is produced using sequence from patent WO2018071676A1
†YTE, 3 amino acid substitutions at positions 249, 251 and 253 in the IgG4 heavy chain constant region (M249Y/S251T/T253E); §IC90 - concentration of DNTH103 required to achieve 90% inhibition of 'state activity being measured' i.e., concentration of DNTH103 required to achieve 90% inhibition in a CH50 assay; IV, intravenous; SC, subcutaneous
Dianthus Therapeutics data on file

DNTH103 has superior affinity and pharmacodynamic potency versus riliprubart*

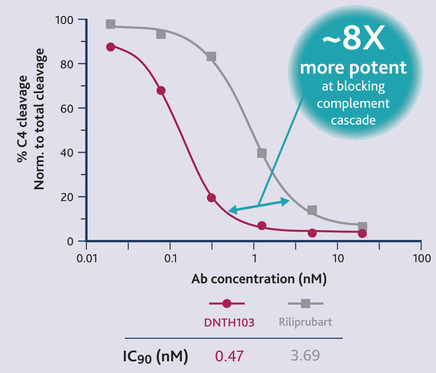
KEY FINDINGS

Affinity assays

		DNTH103	Riliprubart*	Fold improvement
Binding affinity to human active C1s (K_D)[a]	KinExa	9pM	75pM	~8X
	SPR	8pM	35pM	~4X

Enzymatic assay

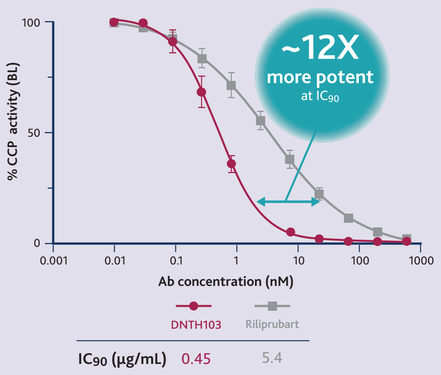
C4 cleavage by human active C1s[b]



IC_{90} (nM)	DNTH103	Riliprubart
	0.47	3.69

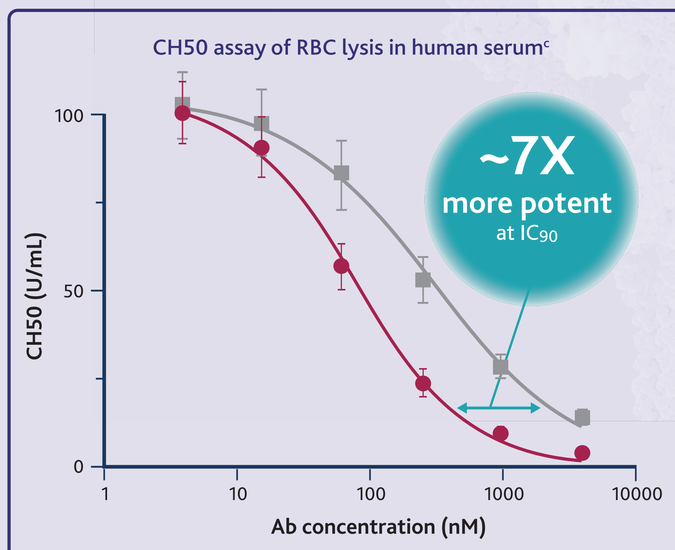
Functional assays of classical pathway inhibition

Wieslab classical pathway assay in human serum[c]



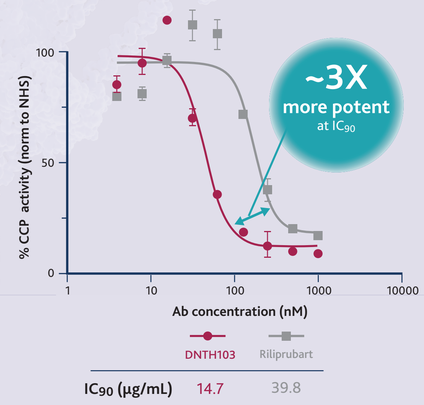
IC_{90} (µg/mL)	DNTH103	Riliprubart
	0.45	5.4

CH50 assay of RBC lysis in human serum[c]



IC_{90} (µg/mL)	DNTH103	Riliprubart
	98	668

Liposome lysis in human serum[c]



IC_{90} (µg/mL)	DNTH103	Riliprubart
	14.7	39.8

DNTH103 consistently outperforms riliprubart* in affinity and potency when compared head-to-head across multiple *in vitro* experiments

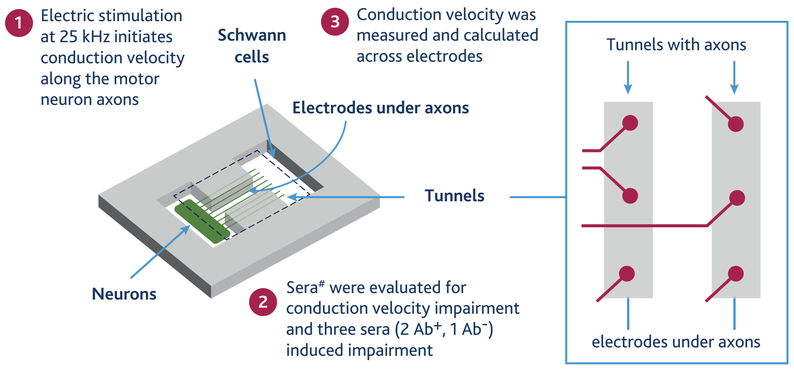
*Riliprubart is produced using sequence from patent WO2018071676A1; [a]Data shown are dissociation constant (K_D) and the average of three different experiments performed at independent laboratories; [b]Data are quantitative analysis of active C1s protease inhibition of cleaved C4 fragments in the presence of DNTH103 or riliprubart; [c]Data shown are the average of three experiments conducted for each of the functional assays (CH50 hemolysis, Wieslab and Liposome). CH50 and Wieslab were confirmed at independent laboratories.

Ab, antibody; BL, baseline; CCP, classical complement pathway; CH50, hemolytic complement assay; NHS, normal human serum; RBC, red blood cell; SPR, surface plasma resonance

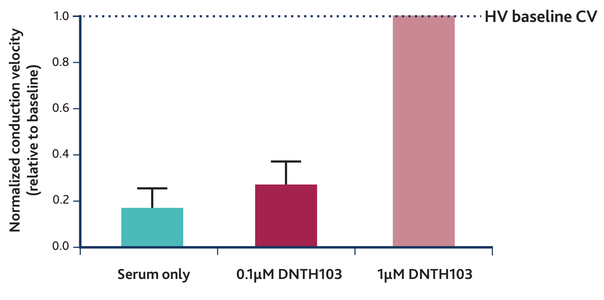
RESULTS

Preclinical evaluation of DNTH103 in an established *in vitro* model of CIDP[10]

- Serum from three CIDP patients was evaluated in a validated commercially available *in vitro* CIDP model
- Endpoint: DNTH103 was evaluated at two doses, results were characterized relative to baseline conduction velocity determined in sera from healthy volunteers (n=3)



DNTH103 restores neuronal conduction velocity in a CIDP model, providing rationale for further scientific development‡



- Average of three CIDP patient samples
- All samples contain 10% human serum
- One-way ANOVA multiple comparison statistical analysis

#Three sera were positive for NF155 (autoantibody test panel: NF155, NF186, CNTN1, CASPR1); ‡Dianthus Therapeutics data on file
Ab^+, antibody positive; Ab^-, antibody negative; ANOVA, analysis of variance; HV, healthy volunteer; CV, conduction velocity

CONCLUSIONS

DNTH103 completely restores conduction velocity across the axons of human motor neurons in the presence of pathological autoantibodies from CIDP patient sera

DNTH103 selectively inhibits the classical pathway with the potential to be safer than less specific complement therapies that also block the lectin and/or alternative pathways

DNTH103 has an extended half-life, and has the potential for patient-friendly, infrequent, low-volume, SC self-administration

CIDP study expected to initiate in H2 2024

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