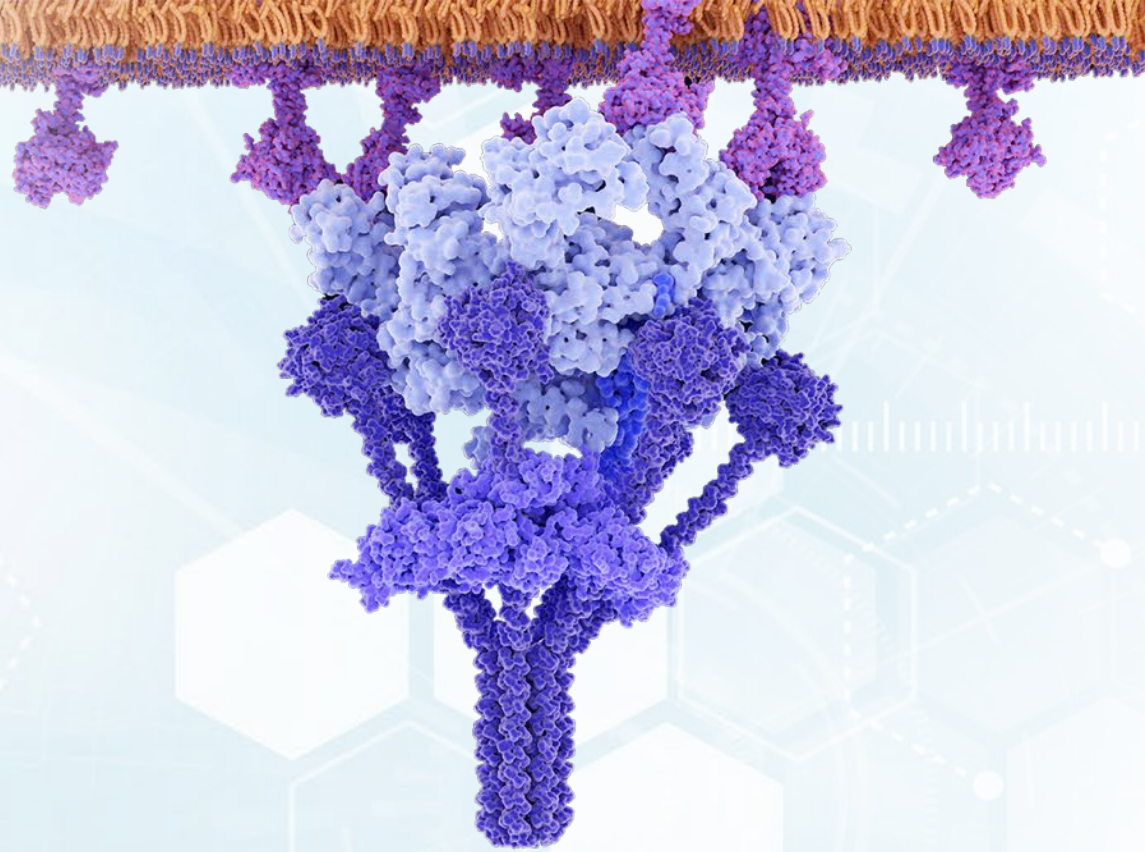

DNTH103: Preventing Nerve Damage in a CIDP Model via Sustained Complement Inhibition

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Presentation at the Annual Meeting of the European Academy of Neurology, 29 June - 02 July 2024, Helsinki, Finland

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- Tina Dysgaard has been a consultant and received research support from the following companies: Astra Zeneca, Alnylam, and Immunovant

C1s is a novel, development-stage target for complement-mediated nerve damage in 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 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 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 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]

CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; MAC, membrane attack complex; IVIg, intravenous immunoglobulin; CSF, cerebrospinal fluid; FcRn, neonatal Fc receptor; IgG, immunoglobulin G; IgM, immunoglobulin M

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]

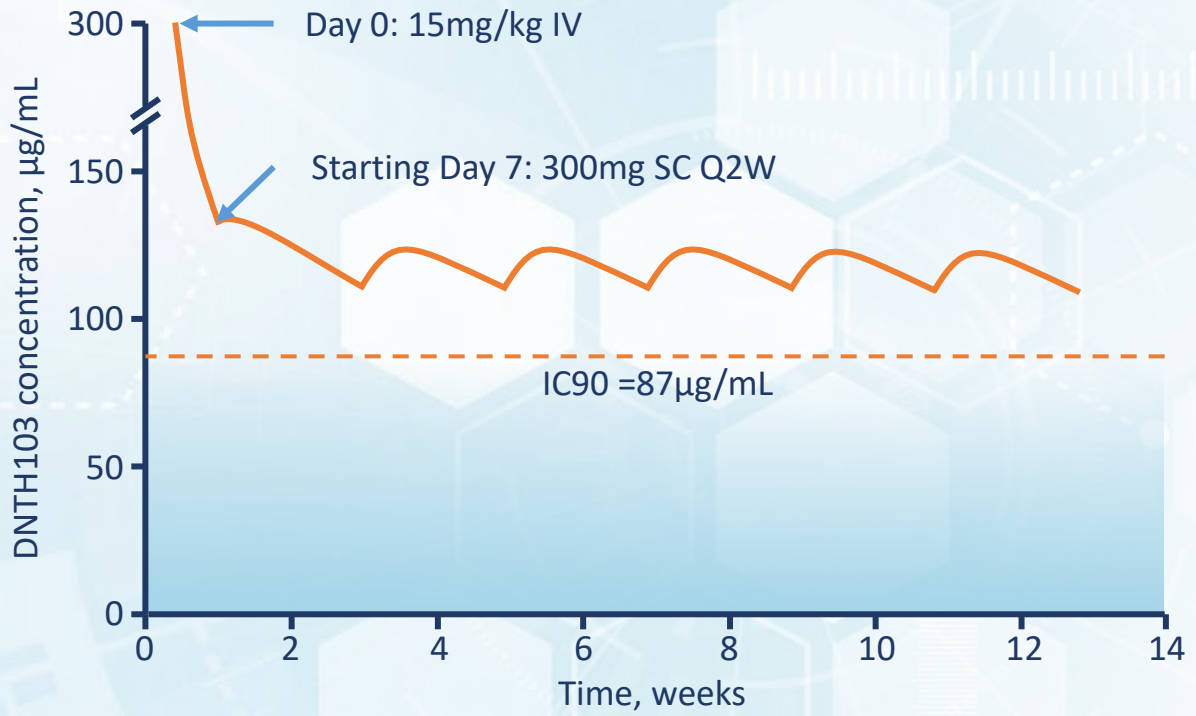
- Humanized anti-C1s monoclonal antibody Riliprubart* showed positive results in a Phase 2 proof-of-concept study in 43 patients with CIDP[9]
- Two Phase 3 studies of Riliprubart* were initiated in CIDP in 2024 (NCT06290141 and NCT06290128)

* Riliprubart is produced using sequence from patent WO2018071676A1

1. Querol LA, et al. Neurotherapeutics 2022;19:864–73; 2. Hays AP, et al. J Neuroimmunol 1988;18:231–44; 3. Couves EC, et al. Nat Commun 2023;14:890; 4. Quast I, et al. Ann Clin Transl Neurol 2016;3:730–5; 5. Yan WX, et al. Ann Neurol 2000;47:765–75; 6. Dalakas MC, Engel WK. Arch Neurol 1980;37:637–40; 7. Dunkelberger JR, Song WC. Cell Res 2010;20:34–50; 8. Querol L, et al. J Peripher Nerv Syst 2023;28:276–85; 9. Querol LA, et al. AANEM 2023;P144.

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
- A global Phase 2 study in gMG is ongoing and global studies in CIDP and MMN are planned to start in 2024



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

IgG, immunoglobulin G; SC, subcutaneous; YTE, 3 amino acid substitutions at positions 249, 251 and 253 in the IgG4 heavy chain constant region (M249Y/S251T/T253E); gMG, generalized Myasthenia Gravis; CIDP, Chronic Demyelinating Polyneuropathy; MMN, Multifocal Motor Neuropathy; IC 90 - 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

Dianthus Therapeutics data on file

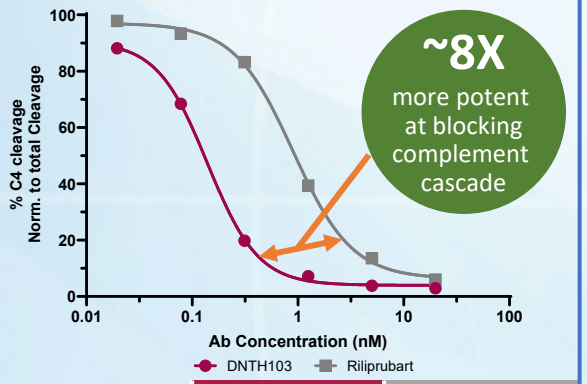
DNTH103 has superior affinity and pharmacodynamic potency vs. Riliprubart*

Affinity assays

		DNTH103	Riliprubart*	Fold Improvement
Binding Affinity to human active C1s (K_D)[1]	KinExa	**9pM**	75pM	**~8X**
	SPR	**8pM**	35pM	**~4X**

Enzymatic assay

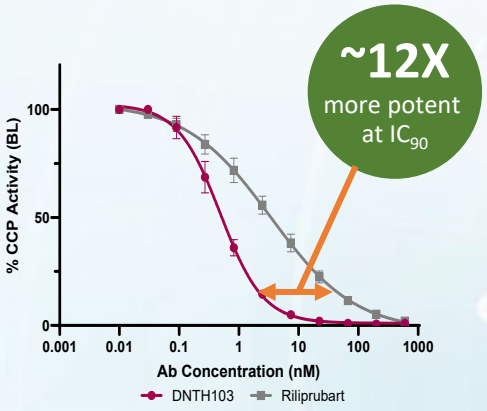
C4 cleavage by human active C1s[2]



	DNTH103	Riliprubart*
IC_{90} (nM)	**0.47**	3.69

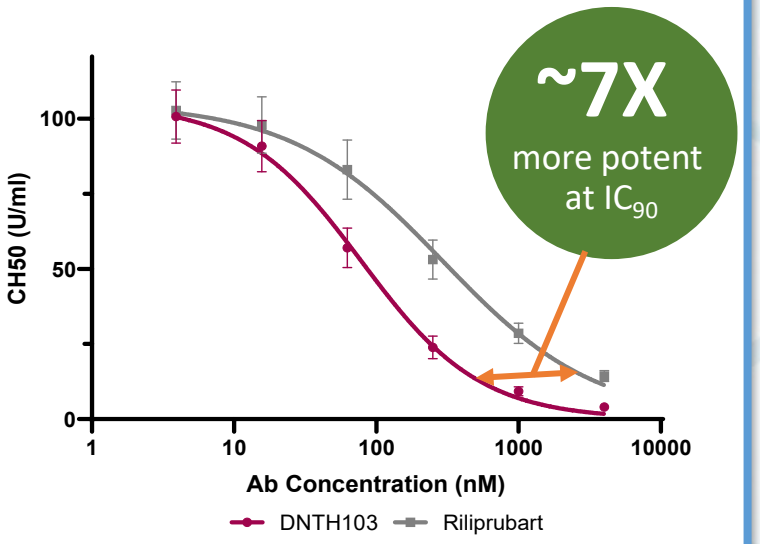
Functional assays of classical pathway inhibition

Wieslab classical pathway Assay in human serum[3]



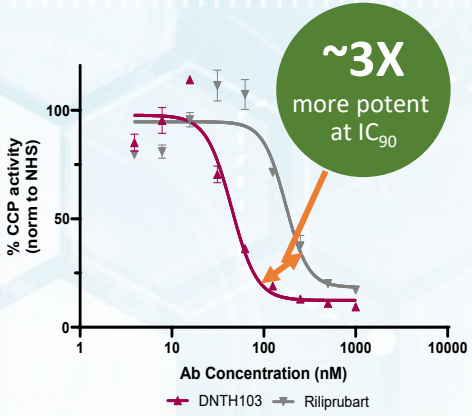
	DNTH103	Riliprubart*
IC_{90} (ug/mL)	**0.45**	5.4

CH50 assay of RBC lysis in human serum[3]



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

Liposome lysis in human serum[3]



	DNTH103	Riliprubart*
IC_{90} (ug/mL)	**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

1 Data shown is dissociation constant (K_D) and the average of 3 different experiments performed at independent laboratories

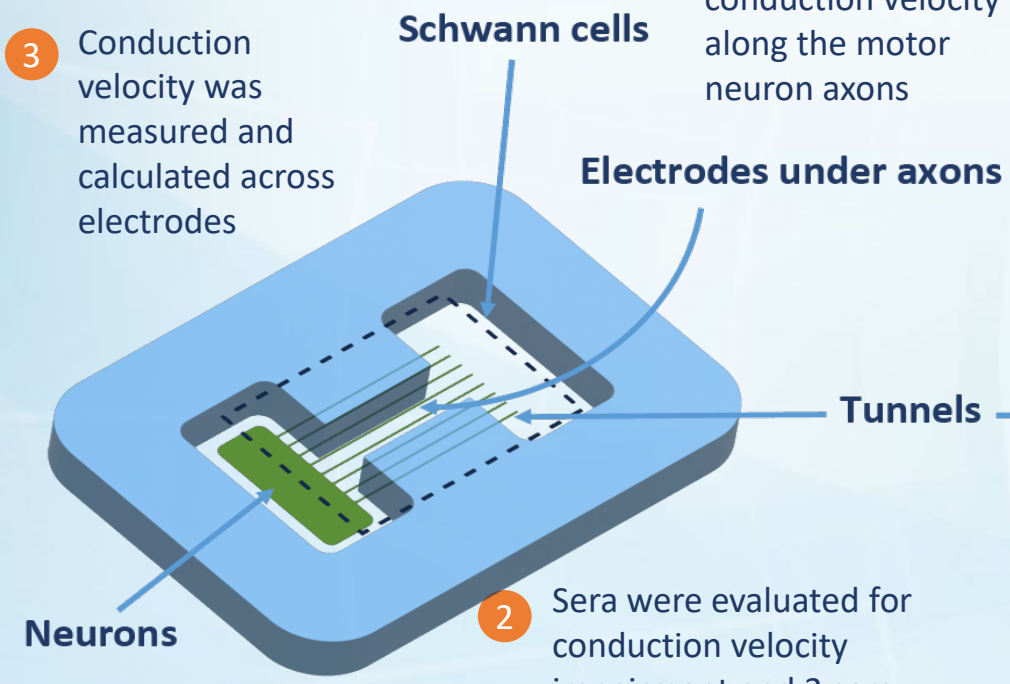
2 Data is quantitative analysis of active C1s protease inhibition of cleaved C4 fragments in the presence of DNTH103 or Riliprubart

3 Data shown are the average of 3 experiments conducted for each of the functional assays (CH50 hemolysis, Wieslab and Liposome). CH50 and Wieslab were confirmed at independent laboratories

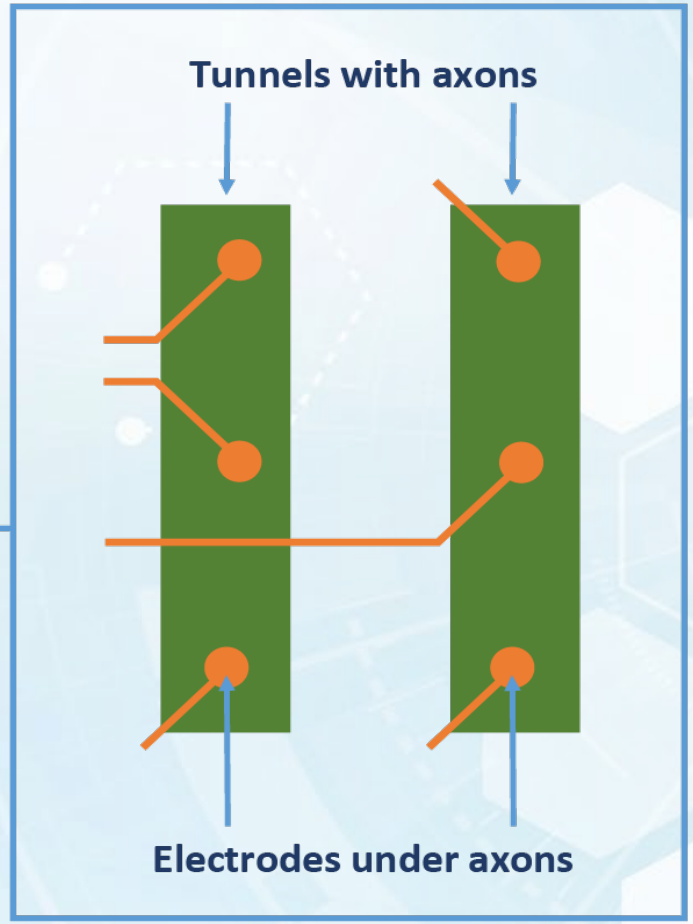
Preclinical evaluation of DNTH103 in an established *in vitro* model of CIDP

1 Electric stimulation at 25 kHz initiates conduction velocity along the motor neuron axons

3 Conduction velocity was measured and calculated across electrodes



2 Sera were evaluated for conduction velocity impairment and 3 sera (2 Ab^+, 1 Ab^-) induced impairment

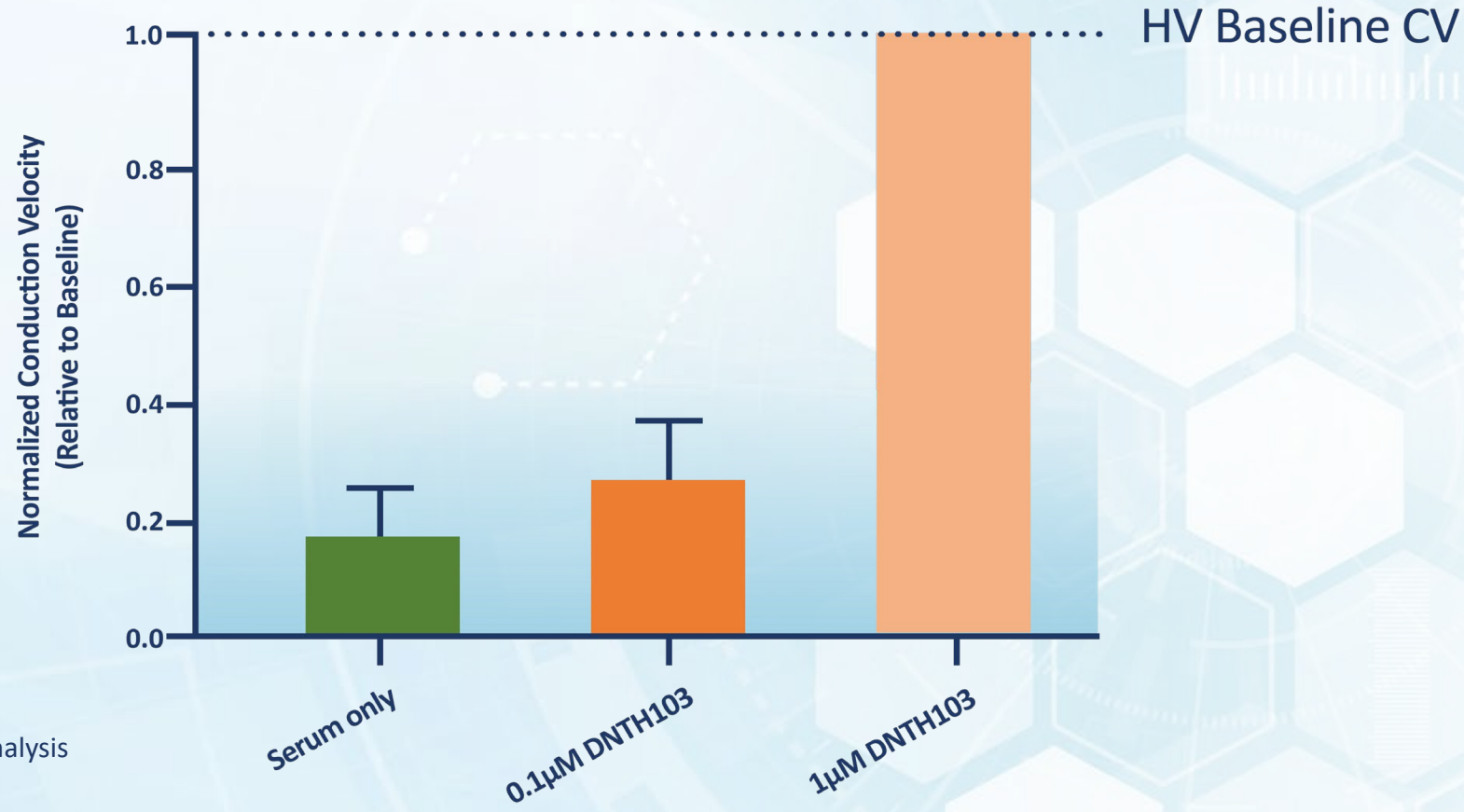


- Serum from 3 CIDP patients was evaluated in a validated commercially available *in vitro* CIDP model
- Endpoint: DNTH103 was evaluated at 2 doses, results were characterized relative to baseline conduction velocity determined in sera from healthy volunteers (n=3)

CIDP, Chronic Inflammatory Demyelinating Polyradiculoneuropathy
Ab+, antibody positive; Ab -, antibody negative; 3 sera were positive for NF155 (autoantibody test panel: NF155, NF186, CNTN1, CASPR1)

Dianthus Therapeutics data on file

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



Average of 3 CIDP patient samples
All samples contain 10% human serum
One-way ANOVA multiple comparison statistical analysis

CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; HV, healthy volunteer; CV, conduction velocity

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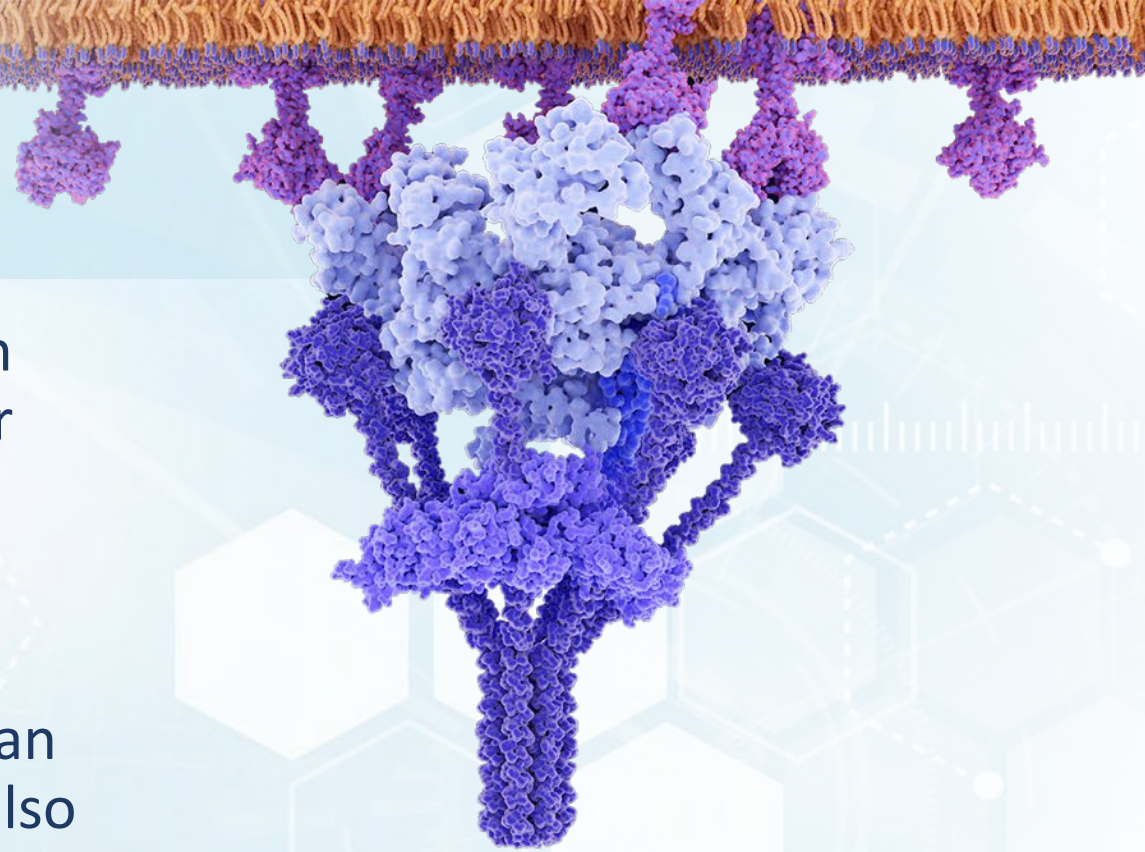
Conclusions



- 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

CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; SC, subcutaneous

Dianthus Therapeutics data on file