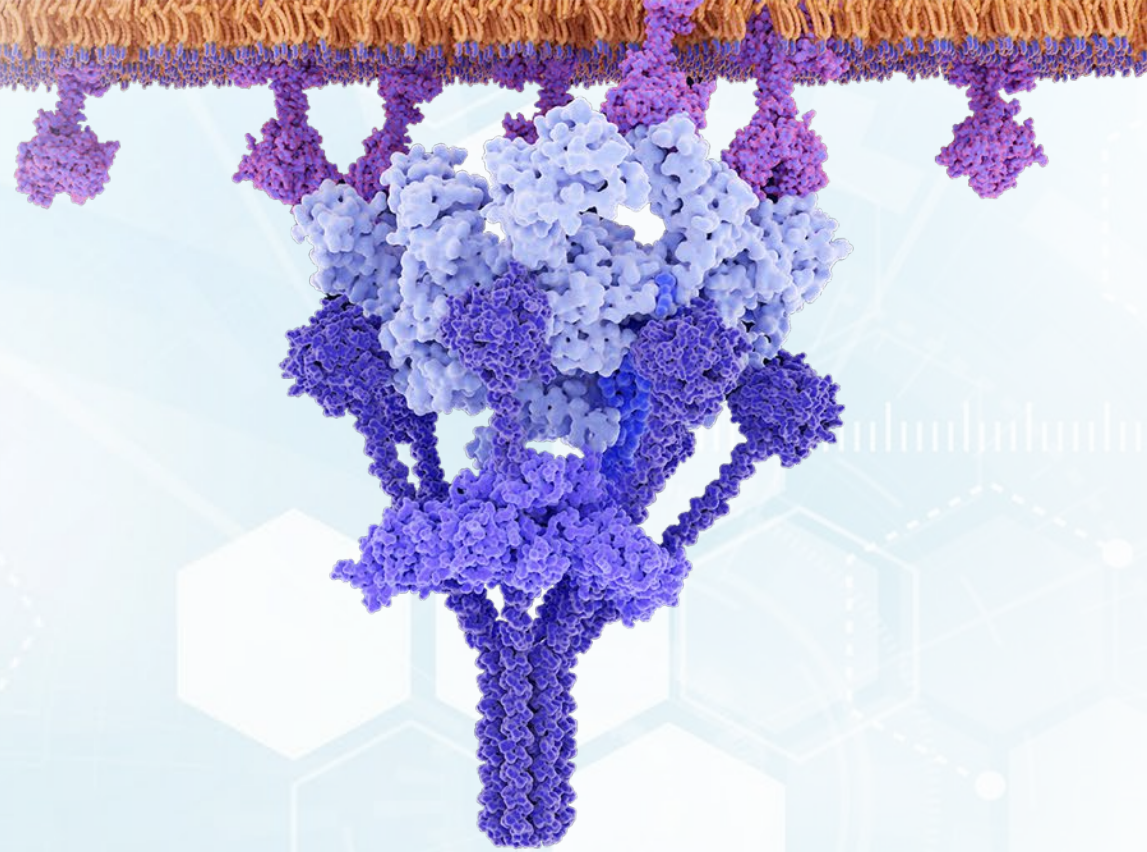
Classical Pathway Inhibition with Anti-Active C1s Antibody DNTH103 Prevents Neurotransmission Impairment in a Preclinical Model of Myasthenia Gravis



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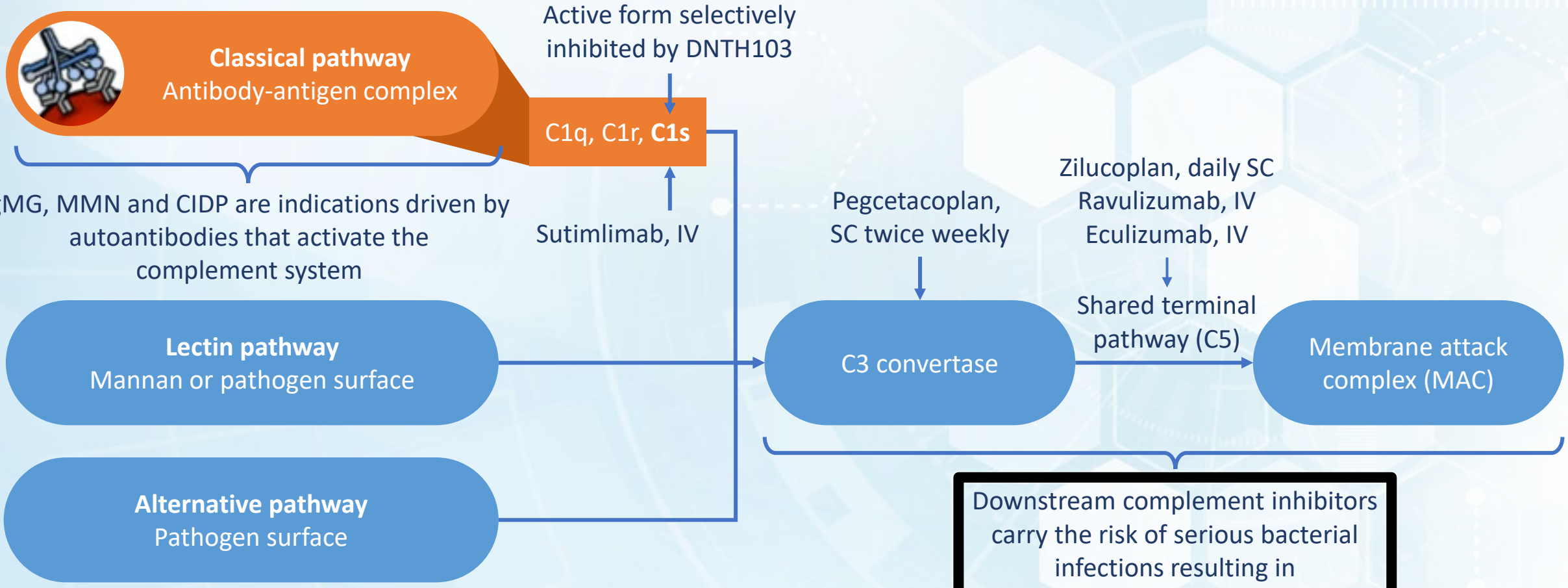
- Sankalp Gokhale is an employee of Dianthus Therapeutics, Inc.

Complement inhibitors are well established in gMG and other severe autoimmune disorders

Targeting C1s preserves immune activity of the lectin and alternative pathways, with the aim to provide a safe therapeutic option



gMG, generalized Myasthenia Gravis; MMN, Multifocal Motor Neuropathy; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; IV, intravenous; SC, subcutaneous; FDA, Food and Drug Administration

Complement inhibitors are well established in gMG and other severe autoimmune disorders

There remains an unmet need for complement inhibition that targets the classical pathway, preserves the critical immune activity of the alternative and lectin pathways, and enables infrequent, convenient SC self-administration

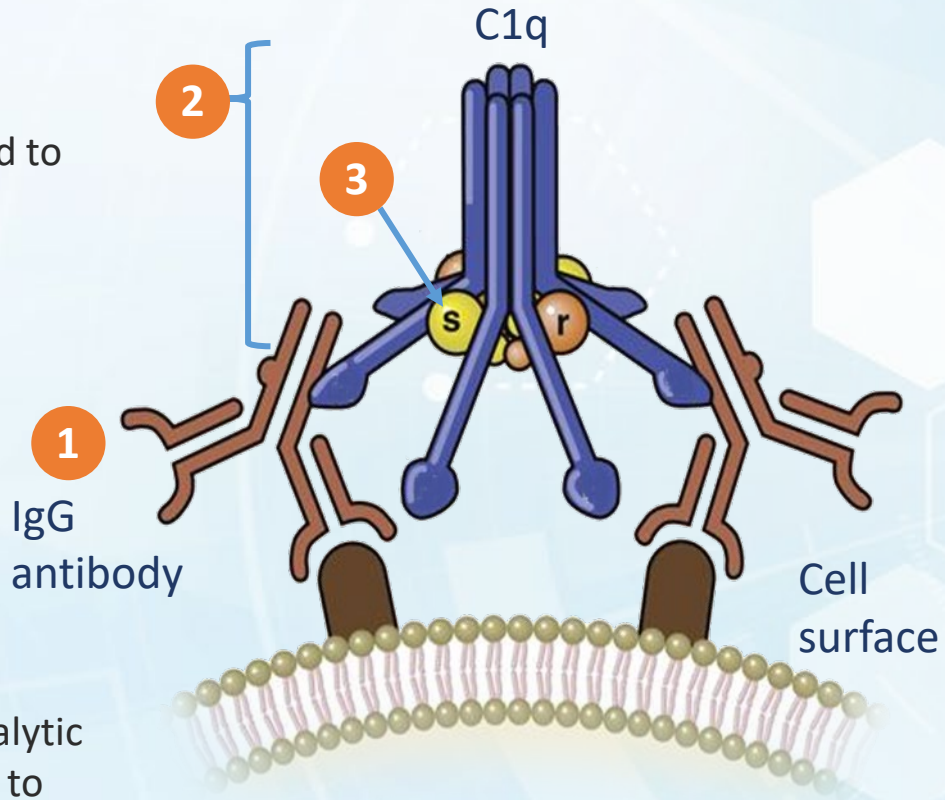
gMG, generalized Myasthenia Gravis; SC, subcutaneous

C1s is a clinically validated target in the classical complement pathway with an FDA approved therapy

1 Classical pathway
The only pathway activated by the presence of IgG and IgM, which bind to the **C1 complex**

2 The C1 complex
The initial component of the classical complement pathway consisting of C1q, C1r and C1s

3 Active C1s
A serine protease that executes catalytic function of the C1 complex, leading to MAC formation



C1s is the only target of the C1 complex with an FDA-approved therapy

Sutimlimab, FDA approved in 2022 for CAD and without a boxed warning against infections from encapsulated bacteria, is a C1s inhibitor but is not selective to the active form and is dosed IV at 6,500–7,500mg every two weeks[1]

Active C1s inhibition has recently demonstrated clinical benefit in CIDP

Riliprubart results show clinical proof of concept for inhibiting active C1s in autoimmune neuromuscular diseases[2]

FDA, Food and Drug Administration; IgG, immunoglobulin G; IgM, immunoglobulin M; MAC, membrane attack complex
CAD, cold agglutinin disease; IV, intravenous; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy

1. Sutimlimab Prescribing Information
2. Querol L, et al. AANEM 2023, Poster 144

DNTH103 – 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 and that could potentially result 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 Phase 2 trials in CIDP and MMN are planned to start in 2024

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

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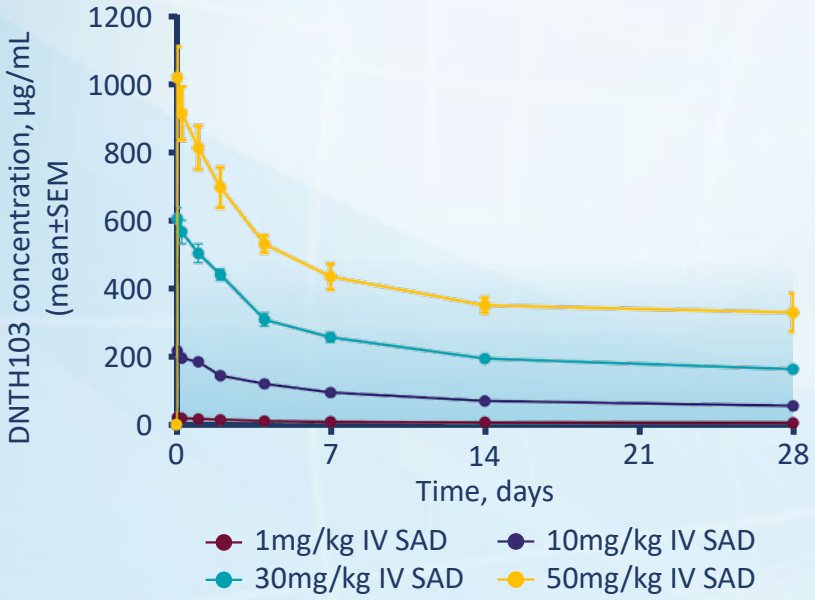
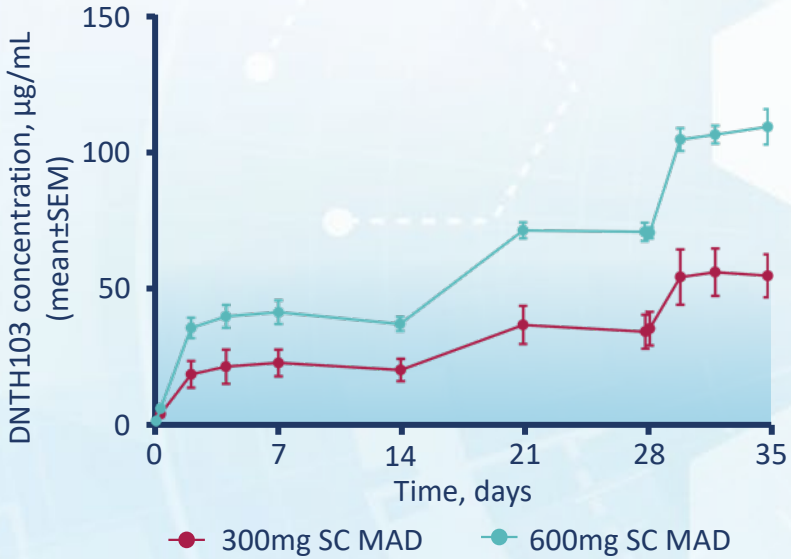
DNTH103 has demonstrated deep and sustained complement inhibition in healthy volunteers

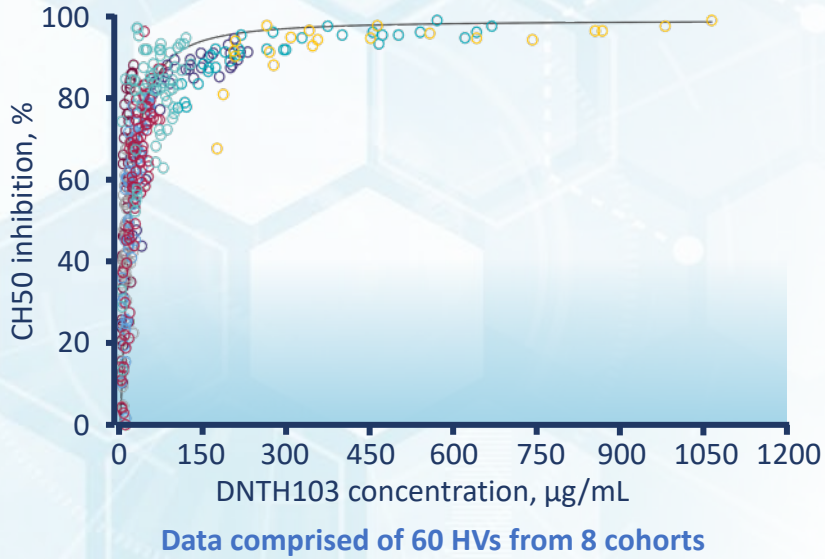
IV SAD:
Linear PK with exposure proportional across doses

SC MAD:
Strong accumulation with Q2W dosing

PK/PD:
Analysis demonstrates IC90 of 87µg/mL







Data comprised of 60 HVs from 8 cohorts

DNTH103 was generally well tolerated
No SAEs, no complement-related infections seen in healthy volunteers

IV, intravenous; SAD, single ascending dose; PK, pharmacokinetics; SC, subcutaneous; MAD, multiple ascending dose
Q2W, once every 2 weeks; PD, pharmacodynamics; CH50, hemolytic complement assay; SEM, standard error of the mean
HVs, healthy volunteers; SAEs, serious adverse events

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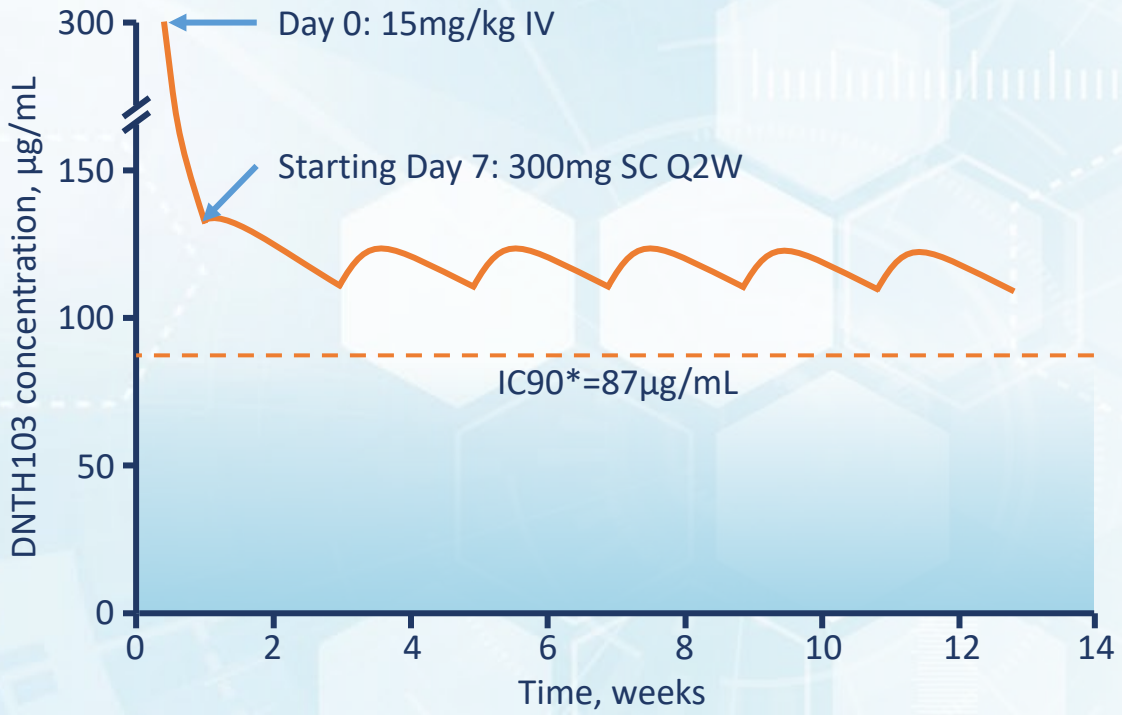
DNTH103 Phase 1 data confirm potent inhibition of the classical pathway as a Q2W 300mg SC injection

- Phase 1 data confirm
  - ~60-day half-life
  - IC90 calculated at 87µg/mL
- Dosing modeled
  - 15mg/kg IV on Day 0
  - 300mg SC Q2W starting Day 7
- High selectivity and potency
  - >10,000-fold increase in binding affinity for active C1s versus proC1s
  - Picomolar binding affinity
- DNTH103 showed dose-dependent inhibition of the classical pathway measured by CH50 inhibition and Wieslab® assay



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

*PK/PD model generated from human phase 1 trial for CH50 data
Q2W, once every 2 weeks; SC, subcutaneous; IV, intravenous; CH50, hemolytic complement assay
PK, pharmacokinetic; PD, pharmacodynamic

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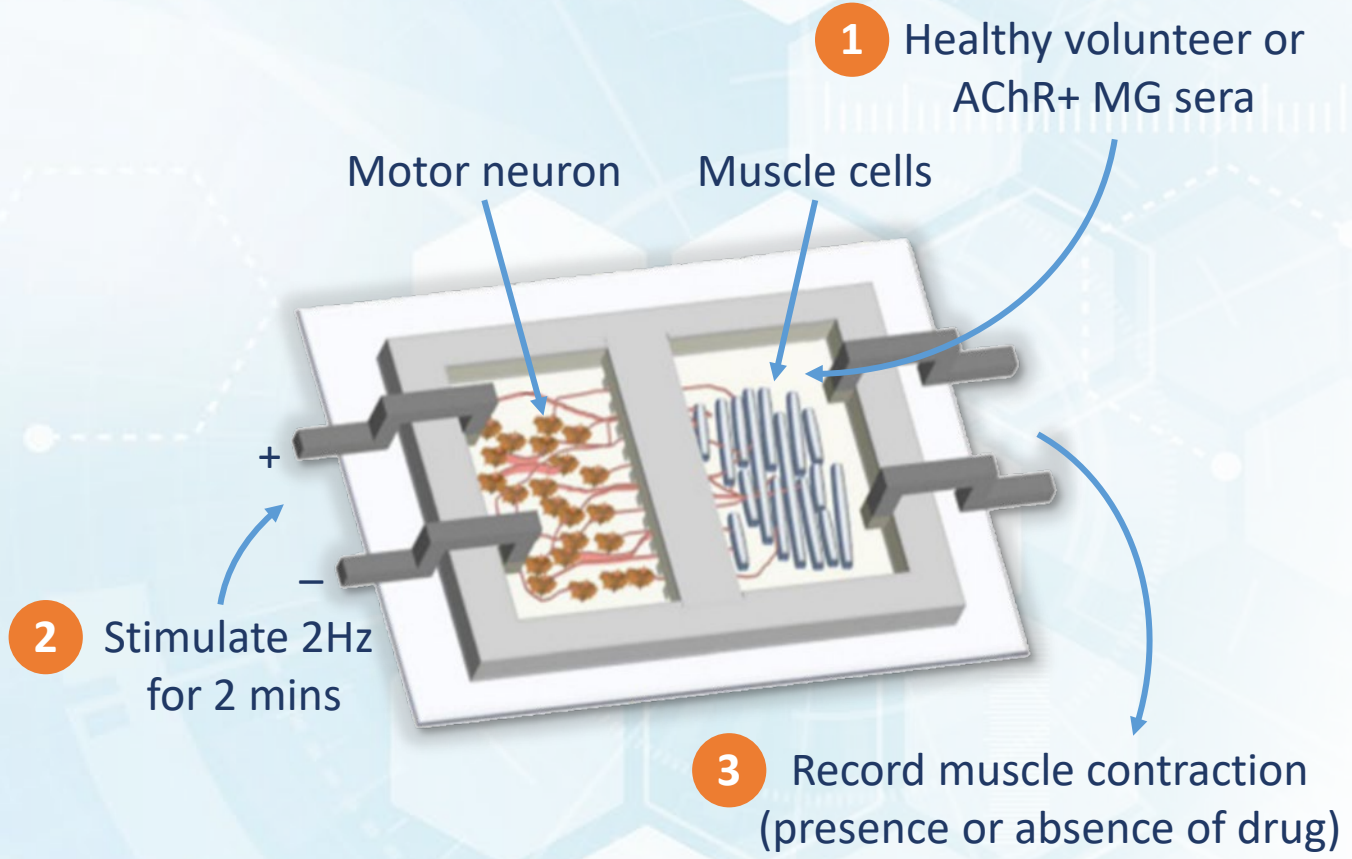
Preclinical evaluation of DNTH103 in an established in-vitro model of MG

- Serum from MG patients used in a validated commercially available humanized in-vitro MG model[1,2,3] simulating a relevant clinical phenotype of impaired neurotransmission and muscle contraction
- 7 MG patient sera samples were collected; 3 were AChR+ and used in the study
- Evaluated response to anti-C5 antibody[§] and DNTH103 via fatigue index (measures neurotransmission and muscle contraction)
  - A reduction in fatigue index indicates improvement in neurotransmission and muscle contraction



[§]Engineered using the ravulizumab patent sequence
MG, Myasthenia Gravis; AChR+, acetylcholine receptor-positive

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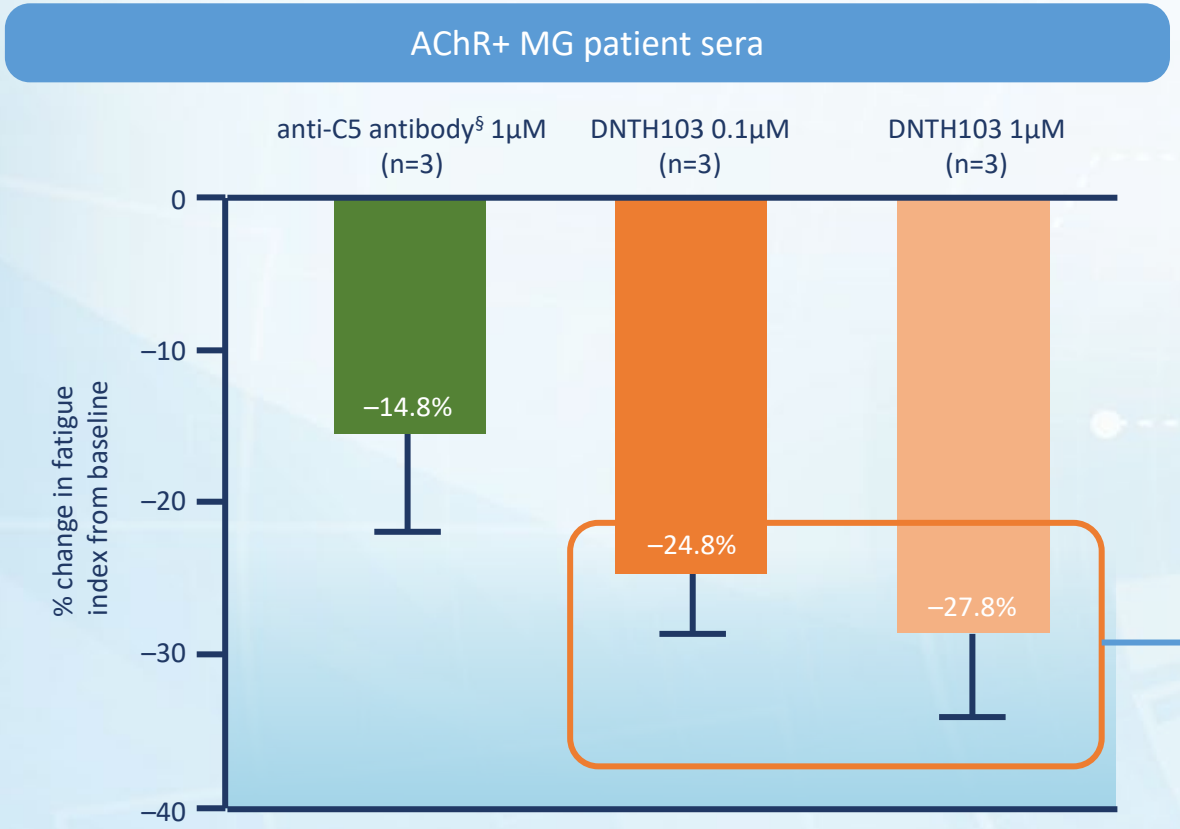
1. Smith VM, et al. Frontiers in Cell and Developmental Biology 2021;9
2. Vila OF, et al. Expert Opinion on Drug Discovery 2019;15:307–17
3. Vila OF, et al. Theranostics 2019;9:1232–46

DNTH103 improves neurotransmission and muscle contraction in an AChR+ MG model† (change from baseline)



Results provide further scientific rationale for DNTH103 in gMG

†Validated in healthy volunteer sera; §engineered using the ravulizumab patent sequence
AChR+ MG, acetylcholine receptor-positive Myasthenia Gravis; MG, Myasthenia Gravis; gMG, generalized Myasthenia Gravis

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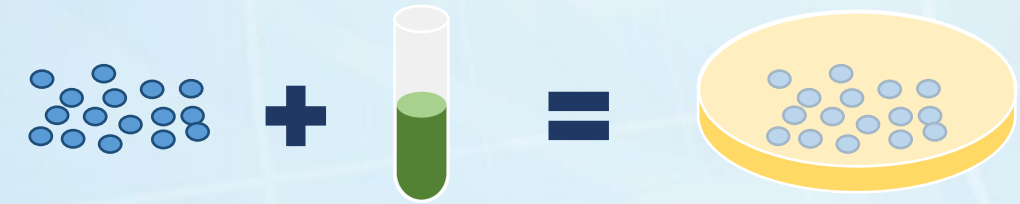
DNTH103 in-vitro study demonstrates lower risk of *Neisseria meningitidis* infections

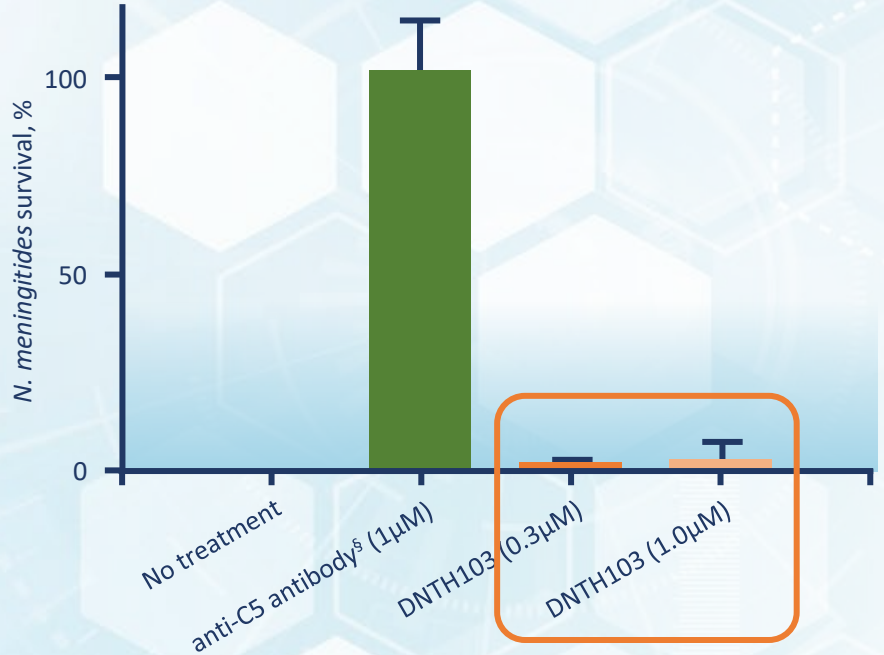
Summary

N. meningitides Sera* + DNTH103 No bacterial survival (complement-mediated killing)



N. meningitides Sera* + anti-C5 antibody§ Bacterial survival (no complement-mediated killing)

N. meningitidis bacterial killing is **unaffected** despite inhibition of the **classical pathway**



In this assay, DNTH103 maintained bacterial killing, potentially leading to a decreased risk of infection vs. anti C5 antibody§

*Normal human sera; §engineered using the ravulizumab patent sequence

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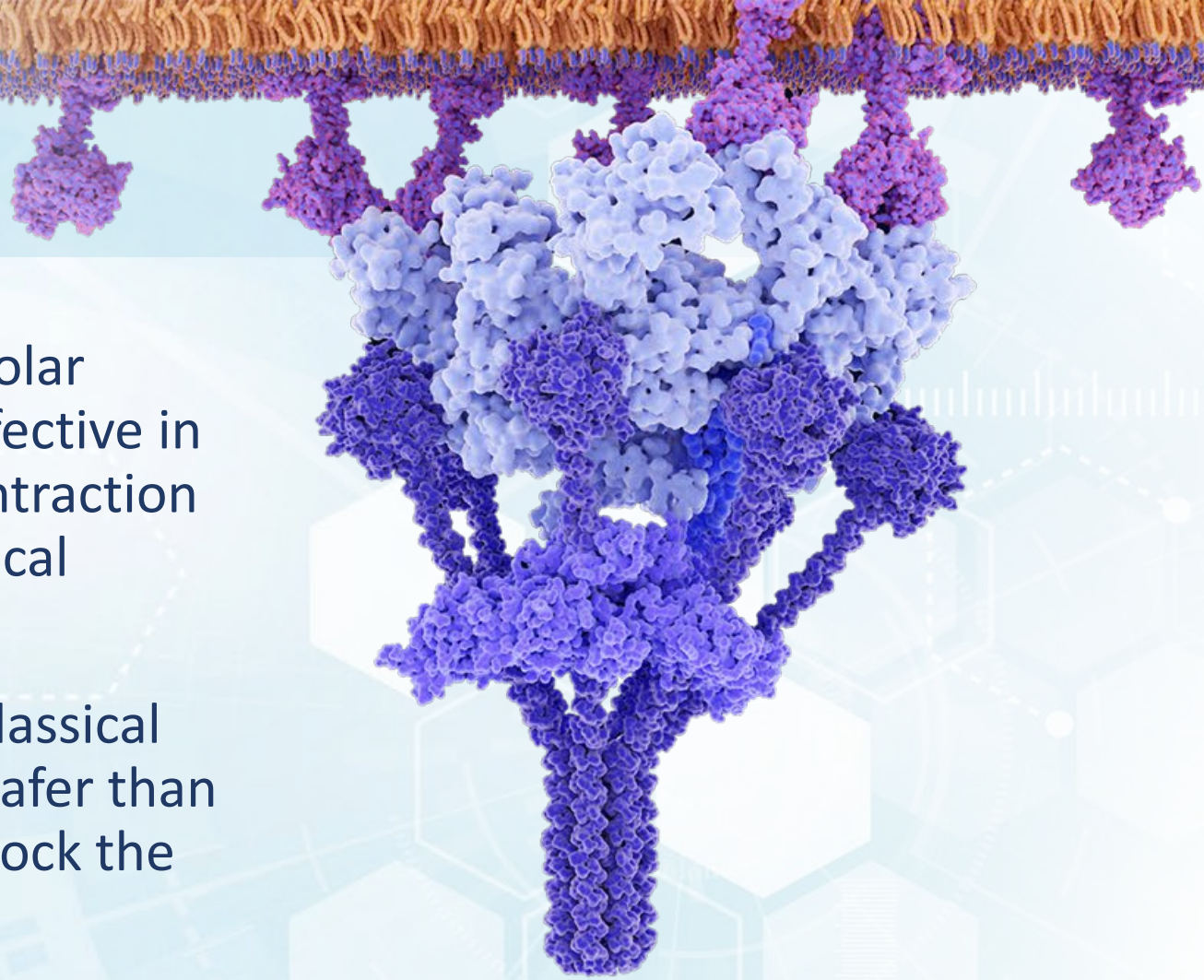
Conclusions



- DNTH103 is a highly potent picomolar inhibitor of active C1s that is as effective in neurotransmission and muscle contraction as an anti-C5 antibody in a preclinical model of Myasthenia Gravis
- DNTH103 selectively inhibits the classical pathway with the potential to be safer than 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

SC, subcutaneous

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