Integrated Applied Clinical Pharmacology in the Advancement of Rare/Ultra-Rare Disease Therapeutics

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Disclosure

I am a full-time employee of Rallybio LLC and hold an equity interest in Rallybio LLC

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- Despite increased activity, need remains for safe and effective rare/ultra-rare disease therapeutics.
- The biotherapeutic enterprise has a responsibility to meet this need.
- The discovery/development of effective, safe and favorably tolerated rare/ultra-rare disease therapeutics faces a number of challenges.
- Integrated applied clinical pharmacology is central to overcome many of these challenges.
- This presentation will comment on challenges and learnings from the development programs of:
  - asfotase alpha for the treatment of hypophosphatasia (HPP); and
  - anti-C5 for the treatment of generalized myasthenia gravis (gMG).

Selected Challenges and Responsive Actions in Understanding the Clinical Presentation, Pathogenesis, Progression, and Endpoint Assessment of Rare/Ultra-Rare Disease (1)

Challenge	Responsive Action	Asfotase	Anti-C5
– Rare/ultra-rare diseases almost always poorly understood/ researched. – This extends to preclinical/ clinical areas.	– Deepen understanding of the clinical disease, its course, and associated morbidities.	√	√
	– Develop preclinical disease models that mimic disease to inform physiology and pharmacology. • Develop systems models to understand target exposure and binding. • Extend to models of preclinical efficacy/toxicity. • Translate preclinical to clinical.	√	√
	– Initiate informative natural history studies. • Requires close partnerships. • Longitudinally assess relevant Pd parameters. Provides the foundational basis for disease models and Bayesian Objective Performance Criteria.	√	

Selected Challenges and Responsive Actions in Understanding the Clinical Presentation, Pathogenesis, Progression, and Endpoint Assessment of Rare/Ultra-Rare Disease (2)

Challenge	Responsive Action	Asfotase	Anti-C5
– Almost always without study design precedent. – Assessment tools are imported and logically applied; almost never validated in the rare disease. – Irreversible morbidity/ mortality may constrain design/ analytical approaches	– Use applied clinical pharmacology to enhance study design/analytical strength and dose selection. • Use preclinical Pk/Pd from relevant animal models, FIH Pk, and natural history study models, to develop/optimize dose/trial design. • Determine optimal sampling times to increase relevant data collection. • Use dose/exposure-response to understand onset, maintenance, offset. • Use data from all patients/subjects to inform dosing in patient subsets.	√	√
	– Review assessment tools in relevant alternative areas and pre-apply to natural history cohorts	√	

Asfotase Alpha for the treatment of Hypophosphatasia (HPP)

– **Deepen understanding of the clinical disease, its course, and associated morbidities**	**√**

- HPP is a rare genetic disorder caused by loss-of-function tissue non-specific alkaline phosphatase (TNSALP) mutation(s).[1,2]
- HPP is characterized by defective bone mineralization.[1,2]
- Broad phenotypic spectrum reflecting genetic heterogeneity (> 410 variants).[1-4]
- Commonly categorized as: perinatal (onset in utero), infantile (onset < 6 months), juvenile (onset 6 months - 18 years), and adult (onset > 18 years).[1]

- Asfotase alpha development program enrolled infants, children and adults and examined efficacy through biochemical, skeletal, functional, and survival endpoints.
- The consistency of results across the continuum of inter-related endpoints and across all pediatric-onset age groups strengthened support for efficacy in HPP.

1. Whyte, M. *Nature Reviews: Endocrinology* **17,** 233-246 (2016); 2. Millán, J.L., Plotkin, H. *Actual osteol*. **8,** 164-182 (2012); 3.Fraser, D. Am. J. Med. 22, 730-746 (1957); 4. Liu, M. et al. Orphanet J. Rare Dis., 16, 159-172 (2021);

Asfotase Alpha for the treatment of Hypophosphatasia (HPP)

–	**Develop preclinical disease models that mimic disease progression to inform physiology and pharmacology**	**√**

- Asfotase is a fusion molecule that binds to hydroxyapatite 32-fold more than unmodified TNSALP.[1]
- TNSALP gene knockout (KO) mice showing < 1% of serum TNSALP activity.[2,3]
- Asfotase administered to KO mice showed clear efficacy at 8.2 mg/kg/day.[4]
- Pd models showed ~3 mg/kg/day as mouse ED80 with maximum at 6-8 mg/kg/day.[5]
- Asfotase first administered to 6 HPP adults who received one dose of 3 mg/kg IV, and then either 1/2 mg/kg/wk sc for 3 wks; and, to severe HPP children <3 yrs old at doses up to 3 mg/kg 3x/wk – serum alkaline phosphatase concentrations within pre-clinical efficacy range.[6]
- Asfotase was administered to 11 severe HPP infants/young children (2 mg/kg single IV followed by 3 mg/kg/wk sc for 24 wks). Healing of rickets in 9 patients; all patients showed pulmonary stabilization/improvement, reduced plasma Ppi/PLP.[7]
- Mouse models developed covering the breadth of HPP disease.[8,9]

1. Millán, J.L., Plotkin, H. Actual Osteol. 8, 164-182 (2012); 2. 5. Narisawa, S., Fröhlander, N., Millán, J.L. *Dev Dyn* **208,** 432-446 (1997); 3. Fedde, K.N. *et al.J Bone Miner Res* **14,** 2015-2026 (1999); 4. Millán, J.L. *et al. J. Bone Miner. Res*. **23**, 777–787 (2008); 5. Yadav, M.C. *et al. Bone* **49,** 250–256 (2011); 6. Millán, J.L, Whyte, M.P. *Calcif. Tissue Int.* **98**, 398–416 (2016); 7. Whyte, M.P. *et al.* N. Engl. J. Med. **366**, 904-13 (2012); 8. Hough, T.A. *et al. J. Bone Miner. Res.* **22**, 1397–1407 (2007); 9. de Oliveira, F.A. *et al. JBMR® Plus (WOA)* **7,** e10709 (2023).

Asfotase Alpha for the treatment of Hypophosphatasia (HPP)

– **Initiate informative natural hx studies using ascertained dx criteria**	**√**
– **Review assessment tools in alternative disease areas with relevant disability and pre-apply to selected natural hx cohorts**	**√**

- All asfotase efficacy studies supported by comparison to matched hx controls.[1]
- Studies in perinatal/infantile-onset showed improved overall/ventilator-free survival compared to matched hx control group.[1]
- Studies in juvenile-onset HPP showed functional and radiographic improvement compared to matched hx control group.[1]
- Efficacy of asfotase in juvenile-onset HPP supported by gait improvement using the modified Performance Oriented Mobility Assessment-Gait (mPOMA-G) (originally designed for elderly gait assessment), assessed by video recordings from asfotase-treated and hx matched children.[1]

1. FDA. STRENSIQ (asfotase alfa) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000TOC.cfm (2015). Accessed 18 February 2024.

Asfotase Alpha for the treatment of Hypophosphatasia (HPP)

– Use applied clinical pharmacology to enhance study design/ analytical strength and dose selection	√

- In perinatal/infantile-onset, exposure-dependent increase in overall survival.[1]
- In juvenile-onset HPP patients, exposure-response in multiple Pd measurements, with a plateau at ~1500 - 2000 U/L. [1]
- Impaired TNSALP function causes PPi elevation. PPi is a potent inhibitor of hydroxyapatite mineralization and a potential contributor to weakness and pain.[2]
- Asfotase administration resulted in rapid/sustained PPi decreases with normal levels generally throughout the study.[3]
- Administration of asfotase 9 mg/kg/wk caused PPi levels to decrease below normal in 5/9 patients, suggesting excessive PPi suppression.[4]

- Since asfotase is a bone-targeted fusion protein, systemic alkaline phosphatase exposure has limited translational value for HPP therapeutics of novel design.
- Further understanding relationships among an array of Pd endpoints will assist informed development of new HPP therapeutics.

1. FDA. STRENSIQ (asfotase alfa) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000TOC.cfm (2015). Accessed 16 April 2024; 2. Beck, C., Morbach, H., Richl , P., Stenzel, M., Girschick, J. Rheumatol Int. 29, 229–238 (2009); 3. Rutsch F. et al. Am. J. Pathol. 158, 543-554 (2001); 4. Seefried, L. et al. Bone 142, 115664 (2021).

Anti-C5 for the treatment of generalized Myasthenia Gravis (gMG)

– **Deepen understanding of the clinical disease, its course, and associated morbidities**	**√**

- MG is a rare, acquired autoimmune disorder of the neuromuscular junction (NMJ).[1-3]
- 90% of MG patients have generalized MG (gMG), with 70-80% positive anti-cholinergic receptor (anti-AChR) antibodies (predominantly IgG1/3).[1,2]
- Standard non-complement treatment includes administration of anticholinesterase (eg, pyridostigmine), steroids and immunosuppressive agents.[1]
- The complement cascade is involved in innate/adaptive immune response with classical pathway activation through binding of C1q to the Fc portion of immunoglobulins (esp. IgG1/3) bound to their antigenic target.[4,5]
- Substantive clinical and histopathological data support the role of complement in the pathogenesis of gMG, including ultrastructural demonstration of IgG, complement and the terminal membrane attack complex (MAC) on the NMJ membrane.[1,3,6]

1. Gilhus, N.E. *N. Engl. J. Med*.**375**, 2570-81 (2016); 2. Gilhus, N.E., 2, Skeie, G.O., Romi, F., Lazaridis, K., Zisimopoulou, P., Tzartos, S. *Nature Reviews Neurology* **12**, 259–268 (2016); 3. Howard, J.F. *Ann. N.Y. Acad. Sci.* **1412**, 113–128 (2018); 4. Mastellos, D.C., Ricklin. D., Lambris, J.D. *Nat. Rev. Drug Discov*. **18**, 707–729 (2019); 5. West, E.E., Woodruff, T., Fremreaux-Bacchi, V., Kemper, C. *Lancet* **403,** 392-405 (2024; 22. Sahashi, K., Engel, A.G., Linstrom, J.M., Lambert, E.H., Lennon, V.A. *J. Neuropathol. Exp. Neurol*. **37**, 212-23 (1978).

Anti-C5 for the treatment of generalized Myasthenia Gravis (gMG)

–	**Develop preclinical disease models that mimic disease progression to inform physiology and pharmacology**	**√**

- Two distinct gMG animal models: (1) passive transfer of anti-AChR antibodies; and (2) active immunization with purified AChR proteins.[1,2]
- Complement inhibition (genetic/pharmacologic) effective in prevention/ treatment.[2]
- In passive experimental MG, anti-C5 mAb pretreatment prevented the development of severe weakness and, when administered after the onset of weakness restored strength in two-thirds of the rats.[3]
- gMG studies were conducted with the anti-C5 therapeutics eculizumab and zilucoplan (both inhibiting terminal complement pathway activity):
  - Eculizumab (humanized monoclonal lgG2/lgG4 anti-C5 antibody) and
  - Zilucoplan (15 amino-acid synthetic macrocyclic peptide).
  - Both bind complement protein C5 inhibiting its cleavage to C5a and C5b.[4,5]

1. Toyka, K.V. *et al. N. Engl. J. Med.* **296**, 125-131 (1977); 2. Kusner, L.L.., Sengupta, M., Kaminski, H.J. *Ann. N.Y. Acad. Sci.* **1413**, 136–142 (2018); 3. Zhou, Y., Gong, B., Lin, F., Rother, R.P., Medof, M.E., Kaminski, H.J. *J. Immunol.*. **179**, 8562-7 (2007); 4. FDA. Soliris (eculizumab) for gMG. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/125166Orig1s422.pdf (2017). Accessed 16 April 2024; 5. FDA. Zilbrysq https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216834Orig1s000TOC.cfm (2023). Accessed 16 April 2024.

Anti-C5 for the treatment of generalized Myasthenia Gravis (gMG)

– **Use applied clinical pharmacology to enhance study design/ analytical strength and dose selection**	**√**

Eculizumab

- 14 AChR-Ab+ refractory gMG patients randomized to eculizumab (600 mg/900 mg dose) or placebo in a Phase 2 db crossover trial with 16-wk treatment arms. Efficacy (QMG/MG-ADL) evident by 2 wks in the first period.[1,2]
- 125 AChR-ab+ refractory gMG patients randomized to eculizumab (900 mg/1200 mg dose) or placebo in a 26-wk, db, parallel group trial. While statistical significance was not reached in the 1° endpoint (due to the analytical approach), marked improvement was seen in an array of 2° endpoints (eg, QMG, MG-ADL).[1,3,4]
- Eculizumab drug levels were measured in both trials however cross validation of the analytical methodology was not available, precluding comparison of drug levels.[1]
- Complete terminal complement inhibition (free C5 <0.5 µg/mL) in 98% post-baseline samples in P3, with 116 µg/mL the target level to achieve this.[1,5]
- No evidence of increased efficacy with higher levels of eculizumab suggesting an efficacy plateau.[1,5]

1. FDA. Soliris (eculizumab) for gMG. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/125166Orig1s422.pdf (2017). Accessed 16 April 2024; 2. Howard, J.F. et al. *Muscle Nerve* **48**, 76-84 (2013); 3. Howard, J.F. et al. *Lancet Neurol* **16**, 976-986 (2017); 4. Menon, D., Pincheira, A.U., Bril, V. *Expert Opin. Emerg. Drugs* **26**, 259-270 (2021); 5. Monteleone J.P.R., Gao, X., Kleijn, H.J., Bellanti, F., Pelto, R. *Front. Neurol*. **12**, 696385 (2021).

Anti-C5 for the treatment of generalized Myasthenia Gravis (gMG)

– **Use applied clinical pharmacology to enhance study design/ analytical strength and dose selection**	**√**

Zilucoplan

- 44 patients with AChR-Ab+ mod/severe gMG randomized to zilucoplan 0.1 mg/kg, 0.3 mg/kg, placebo once daily in a 12-wk double-blind Phase 2 study. Efficacy (QMG, MG-ADL) generally similar in zilucoplan 0.1 and 0.3 mg/kg/day. [1,2]
- Complement inhibition (sRBC hemolysis) was 81.8% in patients receiving 0.1 mg/kg and 94.9% in those receiving 0.3 mg/kg.[1,2]
- 174 patients with AChR-Ab+ gMG randomized to zilucoplan 0.3 mg/kg or placebo once daily in a 12-wk P3 db, parallel-group trial with zilucoplan efficacy confirmed.[1,3]
- Complete (<10%) terminal complement inhibition (sRBC hemolysis) was evident in the zilucoplan group throughout the trial.[1,3]

- Zilucoplan was evaluated in 2 12-wk P2 PNH studies, using a 0.3 mg/kg once daily regimen for all patients after wk 2. While sustained complement inhibition was seen, the clinical response in transfusion dependent patients was insufficient.[4]

1. FDA. Zilbrysq https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216834Orig1s000TOC.cfm (2023). Accessed 16 April 2024; 2. Howard, J.F. *et al*. *J.A.M.A. Neurol*. **77**, 582-592 (2020); 3. Howard, J.F. *et al*. *Lancet Neurol*. **22**, 395-406 (2023); 4. Kulasekararaj, A.J. *et al*. *Haematologica* **109**, 929-935 (2024)

Anti-C5 for the treatment of generalized Myasthenia Gravis (gMG)

– **Use applied clinical pharmacology to enhance study design/ analytical strength and dose selection**	**√**

Eculizumab

- Similar improvement in MG-ADL in the Phase 2 and 3 trials, combined with the absence of exposure-response in P3, supports efficacy with the less than maximal C5-targeted terminal complement inhibition. This contrasts with PNH where maximal C5-targeted terminal complement inhibition is needed.

Zilucoplan

- Generally similar efficacy using the lower/higher zilucoplan P2 doses supports the efficacy of < maximal C5-targeted terminal complement inhibition in gMG. This contrasts with PNH where max C5-targeted terminal complement inhibition is needed.

- Additional Pk/Pd data with eculizumab, zilucoplan and other anti-C5 therapeutics will expand the understanding of anti-C5 requirements for the gMG treatment spectrum.

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