Low Dose Interleukin-6 (SON-080) for Neuropathies: Toxicology and Clinical Plans

Susan Dexter[1], Gael Hedou[2], Richard T. Kenney[1], Darrel J. Rezac[3], Pankaj Mohan[1]

[1]Sonnet BioTherapeutics Inc., Princeton, NJ, USA; [2]Sonnet BioTherapeutics CH SA, Switzerland, [3]Latham Biopharm Group, Inc., Elkridge, MD, USA

AAACR Poster #7181 April 2024

Abstract

Neuropathies are conditions in which peripheral nerves degenerate, resulting in sensory and motor symptoms that can profoundly affect the patients' quality of life. Chemotherapy-induced peripheral neuropathy (CIPN) is induced by most antineoplastic agents, affecting cancer patients during or following completion of treatment. Neuropathy-specific pain medication is most often inefficient against pain, can cause major side effects that limit their use, do not address non-pain related symptoms, and do not stop CIPN progression. Most evidence suggests that physical exercise is the most efficient approach to reduce neuropathy symptoms and potentially, progression. Other publications have causally linked exercise, through the ability of contracting muscles to release low levels of interleukin-6 into the bloodstream thereby activating several metabolic and physiological pathways that help regenerate muscle and nerve tissue, affect glucose homeostasis, increase lipolysis, improve microvascular blood flow and reduce inflammation. Preclinical disease models of CIPN and diabetic peripheral neuropathy (DPN) have confirmed that IL-6 administered at low doses is capable of stimulating peripheral nerve growth, thereby ameliorating motor and sensory functions and normalizing the associated pain or sensation disturbance of neuropathy. The maximum tolerated (MTD) dose of recombinant human IL-6 (rhIL-6) has been established as a treatment for thrombocytopenia in hundreds of cancer patients using the drug product that was produced in the 1990's (Process A) dosed intravenously (IV) or subcutaneously (SC). We have developed a cGMP compliant version of rhIL-6 (SON-080) using a state-of-the-art process (Process B) that meets current regulatory guidelines for cell lines and processes. An analytical comparison of SON-080 with Process A rhIL-6 concluded that both drugs are highly comparable for at least 14 different key physicochemical characteristics. Therefore, we expect similar *in vivo* behavior with Process B material as compared with the Process A molecule. In order to support clinical plans for the safety and toxicity of rhIL-6, a dose range and schedule of administration that matches the current clinical protocol was performed in a cynomolgus monkey primate toxicology model. Under these conditions, SON-080 was found safe and well tolerated with a No Adverse Effect Levels (NOAEL) of 30µg/kg, the highest dose tested.On this basis, a fully controlled Phase 1b/2a clinical study, SB211, is ongoing to evaluate safety, tolerability, and efficacy of subcutaneous SON-080 dosage and administration schedule that targets an exposure mirroring the endogenous release levels elicited by moderate to heavy exercise. Confirmation of safety in the first portion of the trial will pave the way for efficacy evaluation with the objective to provide CIPN patients with a novel, safe, and effective treatment for painful neuropathies.

Introduction

IL-6 is a pleiotropic cytokine that participates in the innate immune response (Villar-Fincheira 2021, Geiger 1988; Sproston 2018). The role of IL-6 heavily depends on its body fluid levels. The physiological effects of long lasting, elevated levels of IL-6 are associated with inflammatory states and it potently induces acute-phase proteins, C-reactive protein (CRP), several complement system proteins, and the coagulation cascade. In contrast, transient and limited elevation of IL-6, as induced by normal exercise, reduces inflammation (Pedersen 2017), restores damaged peripheral nerves (Andriambeloson 2006, Callizot 2008), induces hepatic glucose release, and stimulates lipolysis (Pedersen, 2001, Figure 1).

SON-080 is a low-dose rhIL-6 candidate product that is being developed by Sonnet BioTherapeutics as a treatment for CIPN and DPN. These conditions, in which sensory and motor nerve terminals are degenerating, provoke patients' discomfort that can culminate in unbearable pain, as well as distorted sensations and autonomic abnormalities. Antineoplastic drug treatment frequently confers a wide range of neurologic complications. The most common indirect neurologic complication in CIPN is rooted in the dysfunction of motor, sensory and/or autonomic nerves (Starobova 2017; Bonhof 2019; Zajaczkowska 2019). CIPN may also compromise chemotherapeutic treatment of the underlying cancer, thereby jeopardizing the chances of the patient's survival. In many cases, neuropathy once established can often cause pain as well as non-pain-related symptoms that can deteriorate the patient's quality of life. The limited efficacy of pain medications and their side effects limits their use (Bonhof 2019). This, together with the absence of drugs to halt the persistent degeneration of the nerves, constitute a major unmet medical need in both CIPN and DPN. In preclinical studies, rhIL-6 has demonstrated its potential to tackle the effects of neuropathy by stopping nerve degeneration and potentially stimulating nerve regrowth thereby reducing pain and normalizing some of the physiological conditions that have deteriorated due to nerve degeneration. In addition, a large number of pre-clinical toxicology and clinical studies in thrombocytopenia have established the safety and maximum tolerated dose (MTD) in humans.

Sonnet recently initiated a Phase 1b/2a clinical trial in CIPN patients (SB211, NCT05435742) to evaluate the safety, tolerability, and efficacy of repeated subcutaneous administration of SON-080 in patients with persistent CIPN following the end of chemotherapeutic treatment. A GLP toxicology study in cynomolgus monkeys following a dose and administration schedule compatible with that of the clinical trial, preceded the SON-080 CIPN clinical trial.

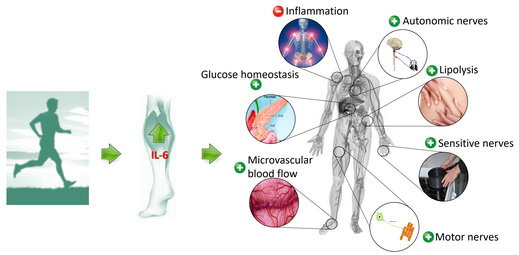


Figure 1. Exercise-induced IL-6. IL-6 production by muscle activity is transient and leads to limited circulating levels. Such physiological regulation induces a large variety of beneficial effects on biological functions including inflammation, glucose homeostasis, lipolysis, microvascular blood flow and nerve regeneration.

CMC

The original cGMP batches IB018 and IB023 (Process A) were produced in Chinese Hamster Ovary (CHO) cells grown in FBS with antibiotics in a semi-perfusion mode. The product was purified on a mAB immunoaffinity column. This molecule is highly stable over decades of -80ºC storage. The Product (Process A), is the historic material used in the current NHP studies and the earlier clinical studies. Sonnet's updated and optimized CHO cell line is independent of FBS and antibiotics and compliant with current regulatory guidelines. The revised, end-to-end 15-day continuous perfusion manufacturing process complies with current cGMP regulations. Analytical comparability was proven between the Process A (clinical batches IB018 and IB023), and Process B (current process) for manufacture of SON-080 (Tables 1-2).

Analytical Comparability

Attribute	Test	Historical standard IB023	Novel GMP rhIL-6 SON-080
Primary Structure	Intact Mass	Comparable	
	Peptide Mapping for sequence coverage		
	Disulfide Bond mapping		
Secondary Structure	Circular Dichroism (Far UV)		
Tertiary Structure	Intrinsic Fluorescence		
	Circular Dichroism (Near UV)		
Purity Analysis	SE-HPLC (PNGaseF treated)	Monomer- 90.3 HMW-9.7%	Monomer-92.8 HMW- 7.2%
	RP-HPLC	99.5%	99.3%
	CE-SDS	77.3%	81.7%
Glycoform Analysis	N-Glycan analysis by HILIC	Lower galactosylation, fucosylation and sialylation and higher mannosylation as compared to IB023	
Identity	SDS-PAGE	Comparable	
	Western Blot		
	cIEF		
Potency	Reporter Gene Assay	95%	107%

Table 1. Analytical comparability of rhIL-6 manufactured with Historical and New process.

Glycoforms	IB018	IB023	S80C22DS01
Total Afucosylation	26.6	27.1	30.3
Total Fucosylation	44.7	48.3	35.0
Total Galactosylation	62.8	67.1	48.1
Total Mannosylation	4.4	3.9	14.7
Total Sialylation	62.1	67.7	30.7

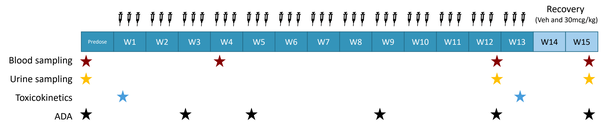
Table 2. Comparison of glycosylation profile between rhIL-6 manufactured with Historical and Current process.

Repeat Dose Toxicology in NHPs

Safety and Toxicology of rhIL-6 were investigated in a Good Laboratory Practices (GLP) Cynomolgus Monkeys (Non-Human Primates, NHP) toxicology study. Process A rhIL-6 was administered SC 3 times per week for 13 weeks at 0 (Vehicle), 1, 10 and 30 µg/kg in males and females (Table 3). A 2-week recovery period was extended to the vehicle and 30 µg/kg cohorts. Toxicity, toxicokinetic parameters and anti-drug antibody (ADA) responses were evaluated. Toxicokinetic parameters were measured at Day 1 and during Week 13 at pre-dose, 1, 2, 3, 4, 6, 8 and 12 hours after dosing. Necropsy was conducted on animals sacrificed on Day 92 (main groups) or Day 106 (recovery groups) and selected organs were weighed, fixed and preserved for histopathology examination.

NHP Toxicology Study Design

Group	SON-080 Dose Vehicle or test item (µg/kg/day)	Main groups Number of Animals and Gender	Recovery groups Number of Animals and Gender
1	Vehicle	4M and 4F	2M and 2F
2	1	4M and 4F	/
3	3	4M and 4F	/
4	30	4M and 4F	2M and 2F



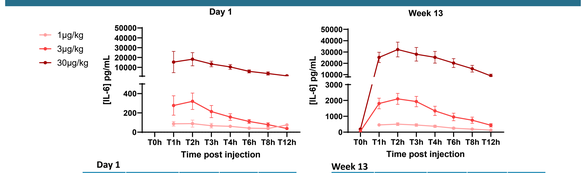
Toxicology and Toxicokinetic parameters evaluated

- Daily monitoring of mortality/morbidity, clinical signs, full clinical examination, body weight, food consumption, ophthalmological examination, cardiovascular and respiratory parameters
- Blood sampling for Hematology/coagulation, clinical chemistry analysis and toxicokinetics
- Serum samples for auto-antibodies (ADA)
- Urinalysis

NHP Toxicology Results

- No rhIL-6 related SAE's (Severe Adverse Events or Dose Limited Toxicities)
- Clinical Examinations
  - No rhIL-6 related changes (body weight, food consumption, ophthalmological examination or blood pressure measurement)
- Hematology and Coagulation: no adverse changes
  - Males
    - Decrease in neutrophils (non dose-related) in males and decrease in WBC in W4 and 13 and in W15 in ½ males @30µg/kg in the main group
    - Very slight decrease in APTT at W13
  - Females
    - Decrease in hemoglobin and hematocrit at W13 only that returned to pre-dose levels at W15
- Clinical chemistry: no adverse changes
  - Changes seen at 3 and 30µg/kg in males and 30µg/kg in females at W4 and W13
  - Increased globulin and/or decreased albumin and A/G ratio
- Urinary parameters
  - No rhIL-6 related changes
- **NOAEL 30µg/kg**

NHP Toxicokinetics



Day 1

Gender	Treatment	Cmax (pg/mL)	Tmax(h)	T1/2 (h)
Males	1µg/kg	95.2	1.5	NA
	3µg/kg	380.3	2.0	3.9
	30µg/kg	23'662.5	1.0	2.7
Females	1µg/kg	75.6	2.0	NA
	3µg/kg	313.5	1.0	4.9
	30µg/kg	17'752.5	2.0	2.4

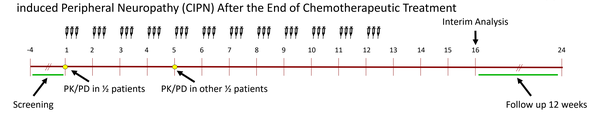
Week 13

Gender	Treatment	Cmax (pg/mL)	Tmax (h)	T1/2 (h)
Males	1µg/kg	548.8	2.0	3.8
	3µg/kg	1'962.0	1.5	4.4
	30µg/kg	23'977.5	2.0	4.6
Females	1µg/kg	464.0	2.0	4.5
	3µg/kg	2'328.8	2.0	6.9
	30µg/kg	40'522.5	2.0	5.2

Overall, the male and female responses to doses over the 13-week study were similar. The C_{max} and AUC_{all} increased in a more than dose-proportional manner. At 1 and 3 µg/kg and in both genders, C_{max} and AUC_{all} were 5 to 12 times higher in Week 13 compared to Day 1. The C_{max} at Week 13 was comparable to Day 1 for males while C_{max} of the females, was 2-3.5 times higher at week 13 than at Day 1. The AUC_{all} was higher in Week 13 for both genders. After test item administration, anti-r-HIL-6 antibodies (ADA's) were detected in serum in all active groups on Day 15 (25/28 animals), Day 29 (27/28 animals) and in one female at 1µg/kg from Day 57 during the treatment period. A dose dependent response was observed for ADA's at the end of the recovery period, with increasing titers on Day 106. Seroneutralizing ADA's were detected in 3 of the 29 animals, including a female on Day 85 and 106, and in a male at Day 57 and a male at Day 85. Note that NHPs often develop ADAs to human cytokines due to the species differences (Villinger 1995). This has not been an issue when other cytokines are introduced in human populations.

Phase 1b/2a clinical study design (ongoing trial)

A Randomized, Double-blind, Placebo-controlled Phase 1b/2a Study to Evaluate the Safety, Tolerability, and Efficacy of Repeated Subcutaneous Administration of SON-080 in Patients with Persistent Chemotherapy-induced Peripheral Neuropathy (CIPN) After the End of Chemotherapeutic Treatment

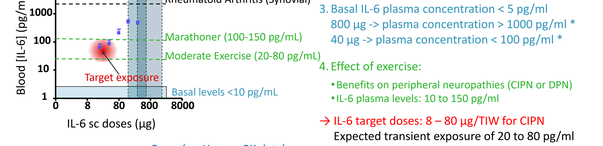


Study design Phase Ib/IIa:

- **Type**: Randomized, Double Blind, Placebo-controlled
- **Population**: 60 persistent (>3months) CIPN adult patients (QLQ CIPN score >3) after chemotherapy (taxane, organoplatin, or vinca alkaloid)
- **Doses**: Placebo, 20 µg, 60 µg, (n=20 per group), SC, three time per week
- **End points**:
  - ***Primary:*** Safety and tolerability
  - ***Secondary:***
    - Pharmacokinetics: C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, $T_{1/2}$, $\%AUC_{extra}$, Vd/F, CL/F
    - Primary efficacy: **Quality of Life CIPN-20 and McGill pain** questionnaires at weeks 5, 9 and 12 and 4 and 12 weeks after treatment arrest
  - Exploratory: Cytokine PD, Change in pain medication, serum Neurofilament L

9 patients are included in the ongoing Phase 1b portion of the trial, in support of safety. Upon positive safety data, the Phase 2a part will recruit the remaining participants to reach 20 patients per treatment group.

Clinical Dose Selection



1. Active dose in Human thrombocytopenia 800 µg/day
2. MTD in human 800 µg/TIW
3. Basal IL-6 plasma concentration < 5 pg/ml
   800 µg -> plasma concentration > 1000 pg/ml *
   40 µg -> plasma concentration < 100 pg/ml *
4. Effect of exercise:
   - Benefits on peripheral neuropathies (CIPN or DPN)
   - IL-6 plasma levels: 10 to 150 pg/ml

→ IL-6 target doses: 8 – 80 µg/TIW for CIPN
Expected transient exposure of 20 to 80 pg/ml

** Data from Serono International*

Previous clinical studies performed by Merck-Serono using the historic version of rhIL-6 (atexakin alfa), and extensive clinical data reported in the literature for IV and SC administration of IL-6 in various patient populations and healthy volunteers, has been well documented. The PK and safety of rhIL-6 are well understood, and the planned dose and schedule of administration in SB211 are expected to provide serum levels that approximate those seen after mild to moderate exercise. Dosing SC intermittently (Three Times in a Week, TIW) prolongs the absorption, lowering the C_{max}, while minimizing adverse events (AEs) . Doses of 20 or 60 µg used in the clinical trial for CIPN will potentially achieve similar human exposures associated with exercise (40 to 80 pg/mL blood).

Conclusions

Sonnet has established a novel efficient production and purification process that is compliant with the current regulatory guidelines, for the manufacture of SON-080. The new SON-080 molecule is highly comparable to the original batches of rhIL-6 made by Merck-Serono. rhIL-6 has demonstrated a high degree of efficacy in restoring degenerated nerves in animal models of neuropathies, proven safe and well tolerated in many preclinical toxicology experiments especially when administered SC, TIW. In particular in monkeys, a NOAEL of 30µg/kg will provide a large enough safety window for human trials. Sonnet's clinical trial in CIPN patients to evaluate primarily safety and tolerability in a Phase 1b was reviewed by the DSMB (Data & Safety Monitoring Board) and found to be 'safe to proceed' to Phase 2a. A follow-on 2a clinical study protocol is approved to provide further safety and efficacy data. Positive results may constitute an important milestone to provide hope for a future safe and efficacious treatment for neuropathies induced by chemotherapy and diabetes, diseases which remain a significant unmet medical need in multiple countries around the world.

Contact

Susan Dexter, Chief Technical Officer, CMC Activities
Sonnet BioTherapeutics Inc.,
SusanDexter@sonnetbio.com

Gael Hedou, PhD, Chief Operational Officer,
Sonnet BioTherapeutics, CH, SA
Ghedou@sonnetbio.com

http://www.sonnetbio.com

References

Villar-Fincheira P, et al., Front Mol Biosci. 8:641734, 2021
Geiger T, et al., Eur J Immunol. 18:717, 1988
Sproston NR, et al. Front Immunol. 9:754, 2018
Andriambeloson E, et al. Neuropathology. 26:32, 2006
Callizot N, et al. Cancer Chemother Pharmacol. 62:995, 2008
Pedersen BK, et al. Curr Opin Hematol. 8:137, 2001
Pedersen BK. Eur J Clin Invest.47:600, 2017
Starobova H, et al. J Exp Med. 218, 2021
Bönhof GJ, et al. Endocr Rev. 40:153, 2019
Zajączkowska R, et al. Int J Mol Sci. 20:14512019
Villinger, F, et al. J Immunol 1995; 155:3946-3954

Scan to access
Sonnet Website