Extending Efficacy and Stability of Ona Botulinum Toxin A with Nano Metallic Silver Tetrahedral Tetraoxide

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ABSTRACT: There are now almost 800 cosmetic and therapeutic clinical applications for the safe and effective injection of Botulinum Neurotoxin ("BONT") and a growing number of new licensees within a market worth more than 4 Billion dollars annually. Despite the rapid growth of the BONT market, there are still two major problems faced by BONT Manufacturers, resellers and healthcare providers namely; 1) BONT's reconstituted with .9% Neutral Buffered Saline (recommended Diluent) have a limited shelf life – they typically last only 7-10-14 days before they begin to degrade and loose efficacy – so wasted product can be extremely costly and 'timely top ups' challenge both clinic and patient schedules. The risks of cross contamination associated with multiple withdrawals from the same vial also prevents /limits their use. 2) Limited efficacy and performance of numerous BONT's ranges from only 10-12 weeks which, for many patients suffering from chronic debilitating, painful ailments such as cervical dystonia, migraines, tension headaches, TMJD, strabismus, clenching and grinding, blepharospasm etc., is not nearly long enough. Patients and healthcare providers both agree that a longer period of time between cosmetic and therapeutics treatments is a treatment option that patients would gladly accept as it means less visits and less injections. Such a technology has huge potential clinical benefits for a wide range of therapeutic treatments so, the impact could affect millions of patients.

Since 2013, several limited phase 1 human clinical trials have been conducted in British Columbia, Canada involving the reconstitution of a Botulinum neurotoxin named Ona Botulinum Toxin A (BOTOX®) (1) with an alternative

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(1) NMSTTO is FDA cleared as a surgical wound wash irrigant and is NOT labeled or approved for Reconstitution with BOTOX® (Ona Botulinum Toxin A). NMSTTO was evaluated as an Off-Label Therapeutic Use and an alternative diluent for BONT under USC 35 – 217. E1 Safe Harbor Exemptions.

diluent to saline called Nanometallic Silver Tetrahedral Tetraoxide ("NMSTTO"). The NMSTTO diluent is an FDA and HPB cleared surgical wound wash irrigant (available in both OTC and Prescription strengths) which has been successfully utilized in thousands of invasive periosseous dental surgeries. There is also long standing safety, efficacy and performance data / clinical reports from hundreds of healthcare professionals; government organizations; teaching universities and peer reviewed publications which all point to the profound wound healing, disinfectant/ antimicrobial preservative nature of this NMSTTO particle. It was based upon numerous validated studies and analytical reports that a cosmetic-based, reconstructive Dentist from Langely, BC., Canada named Dr. Andrew Willoughby determined that the NMSTTO solution could be used safely and effectively as an alternative diluent to reconstitute BOTOX® in a series of off-label limited phase 1 human clinic trials.

The most recent of these human clinical trials took place in 2017 and 2018 and involved 39 healthy, adult participants who were injected with BOTOX® using a new buffered solution ("diluent") comprised of pH adjusted version of the NMSTTO at specific dosages and dilutions. The results of this groundbreaking study were unexpected and unintended. After closely following all 39 participants for over a year and one half from the initial treatment dates, three exceptional observations were made:

1. The muscle relaxing effect of BOTOX® reconstituted with the VeraSIL diluent lasted up to 100+% longer (an average of 5-6 months) in those participants/patients previously injected with just BOTOX® and .9% Neutral Buffered Saline. This meant less injections over time to maintain to the same amount of desired muscle relaxation.

2. The "Bacteriostatic" effect of the VeraSIL diluent helped to preserve the stability of the reconstituted BOTOX® for up to four (4) months while refrigerated - many times longer than with .9% NB Saline.

3. 5 of the 39 patients who had BOTOX® injections (with the NMSTTO diluent) into and around the lips (orbicularis oris muscles) presented at their appointments with HSV-1 outbreaks on their lips. After injecting the BONT into the infected tissue, an accelerated resolution of the Herpetic

lesions was noticed in all 5 participants - total resolution time from time of injection was 6-7 days. The pharmacokinetics behind these findings appear to be closely tied to the wound healing and anti-viral capabilities of the NMSTTO particle.

As of the publication of this Abstract, zero adverse events and no adverse drug reactions were reported by any of the participants.

At the **IMCAS** World International Congress of Cosmetic Dermatologists and Reconstructive Plastic Surgeons in Paris, France in February, 2017, Dr. Willoughby presented details of his earliest clinical findings and explained the pharmacokinetics and a novel cellular mechanism of action for the NMSTTO diluent. Dr. Willoughby explained that the ability to extend the length of time between therapeutic and cosmetic BONT treatments and extend the stability of the reconstituted BONT has significant added value for healthcare providers as well as patients.

American BioTech Labs ("ABL") is the sole manufacturer of a proprietary nano-NMSTTO technology and all uses and applications in the BONT industry for this NMSTTO technology have been exclusively licensed to Dr. WIlloughby's VeraSIL Therapeutics Research company in Langley, B.C., Canada. This NMSTTO particle has a patented solid metallic core which ranges b/w 5-7 Nm in diameter and a resonance frequency (b/w 890-910 TeraHertz the same as Ultraviolet Light A+B frequency). The NMSTTO particle is FDA cleared and HPB approved in various formats. It has a unique silver tetrahedal tetraoxide surface coating that has a powerful, electrostatic, nano-catalytic mode of action, proven to kill a broad range of microorganisms without causing harm to the host or to probiotic bacteria.

The highly charged nature of this crystalline lattice oxide coating on the surface of the solid NanoSilver particle generates its own magnetic field evident in Transitional Electron Microscopy (TEM). We believe that the interaction between the highly charged Ag404 surface coating of the Nanoparticle and the Flagellin locomotor core of the 150kd BONT core is what may be producing these findings of extended efficacy.

There are well over 400 published studies, bacterial and viral challenge tests conducted by over 60 independent companies, labs, universities, and government institutions that demonstrate quick acting 4 and 5 log reductions of the NMSTTO against a wide range of micro-organisms including; Malaria, various Influenza A strains including H1N1, H3N2 & H5N1. Successful in-vitro lab testing has been completed against the HIV lentivirus, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Hepatitis B (effective against both Reverse transcriptase and DNA Ploymerase methods of replication) and *many drug resistant bacteria including C.R.E, M.R.S.A., V.R.E., and all 8 strains of the MDR pleomorphic aerobic gram-negative bacillus Acinetobacter Baumannii so the NMSTTO makes for an excellent preservative / stabilizing agent* especially when human ingestion and animal injection studies show that the NMSTTO is not harmful to human biological tissues. The NMSTTO particle has numerous FDA 510(k) clearances for use as a broad spectrum anti-bacterial agent as a "surgical wound wash and irrigant" and "wound healing hydrogel" as well as a disinfectant for use in medical device insertion sites, surgical incisive wounds, donor and recipient graft sites, burns and other topical lacerations and abrasions. NMSTTO is not a drug and is not metabolized by the body - it is excreted via the liver and kidneys due to particle size.

Over the past 14 and one half years, Dr. Andrew Willoughby, a Dental Surgeon from Langley, BC Canada, has successfully performed in excess of 50,000 Periosseous surgeries with NMSTTO to significantly help reduce pain, inflammation, infection and speed up wound healing in oral surgical sites. It was the combination of no material adverse effects combined with a pressing need for increased efficacy and the aforementioned in vivo and in-vitro data that lead to the proposed use of the NMSTTO as an alternative diluent for reconstitution of the Botulinum Neurotoxin.

Extended efficacy and performance of the Botulinum Neurotoxin has become a major focus for BONT manufacturers who have attempted to address this issue in a number of different ways. Several manufacturers have produced a smaller BONT (less than 900kd) in an attempt to reduce the BONT's "immune profile" and associated immune response. A less pronounced immune

response means that the BONT will take longer to metabolize and it's muscle relaxation effect will last longer but, reported efficacy extension so far, has been less than 4 weeks. Again, the focus has been on **extending efficacy,** which appears to be a real trend in the industry. Yet another contract BONT Manufacturer has intentionally tried to combine its Botulinum Neurotoxin with a complexing protein in the hopes that the body will have a more difficult time breaking down this BONT/oligo-peptide chain combination and thus, the complex will take longer to metabolize and its effect will be prolonged. Despite concerns about additional cell mediated, immunological responses to these constituent proteins, initial tests results using subjective IGA/FWS wrinkle reduction scores show up to 5 months of efficacy. It is important to note that these same BONT Manufacturers have yet to address the issue of extended stability after reconstitution. The NMSTTO diluent (which we refer to as 'VeraSIL") is a completely different technology platform because, it is potentially capable of not only extending efficacy but stability of the BONT as well. In a recent public press release, one of the original Botox Pioneers, Dr. Jean Carruthers, MD, FRCSC, FRC (Opth), has been quoted as saying;

"***I believe my patients will respond favourably to a new Botulinum toxin option that may provide significant wrinkle reduction and extend the window between treatments***".

Dr. Willoughby, DMD, LVIF, FAGD, FICCMO, FICOI, FAACFP, MICCMO and Dr. Mack, MD, PhD (Nano), CPI, FAAPCR have also developed a proprietary method to reverse the extended muscle relaxation effects in case of unintended eyebrow and eyelid ptosis.

This article will focus on the details of Dr. Willoughby's Phase 1 human clinical trial, and upcoming Phase 2 clinical trials which will be overseen by Mack Bio, Inc. It will also provide a plausible explanation of the pharmacology and proposed cellular mechanisms of action for the extended efficacy and stability of OnaBotulinum Toxin A when diluted with NMSTTO.

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