Assessing the safety of TP-102 bacteriophage treatment in the management of diabetic foot infections

Poster# 1690

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Introduction

Chronic non-healing ulcers are a significant medical problem and the incidence of these wounds is to increase as the United States population ages (1). Each year 2-3% of subjects with diabetes will develop a foot ulcer and 15-25% will develop a foot ulcer at least once in their lifetime (2-5).
In current clinical practice the treatment of diabetic foot infections (DFIs) includes debridement and systemic antibiotics. However, because of deficient vascularization and the local microenvironment, antibiotic concentrations are many times sub-therapeutic (6). The incidence of multidrug resistant organisms, namely methicillin-resistant *Staphylococcus aureus* (*S. aureus*) and pan-drug-resistant non-fermenting negative bacilli, is also threatening the outcome of anti-infectious therapy in both community and hospitalized subjects (7). Thus, it is necessary to identify new strategies for the treatment of DFIs.
Bacteriophages are viruses of bacteria that can invade and lyse the bacteria they infect. After their discovery in the early twentieth century, phages were used as therapeutic agents to treat bacterial diseases in people and animals. Currently, as increasing levels of antibiotic resistance leads to the failure of treatments, phage therapy is considered an alternative approach to fight with bacterial infections (8).
Lytic bacteriophages, appropriately complemented by adequate mechanical debridement, could be efficient topical antimicrobial therapy (TAT) agents in some selected clinical environments because of their specificity and efficiency in lysing pathogenic bacteria, even those associated with multidrug resistance. Lytic bacteriophages have also shown efficacy over bacteria in biofilms and action in microaerophilic environments with high bacterial load with no reported pathogenicity to man and animals. Recent animal trials of bacteriophage therapy have demonstrated its potential to heal or improve skin bacterial diseases, both via internal and external applications (9).
Topical treatment has the advantages of avoiding systemic adverse effects, providing increased target site concentration, and allowing the use of agents not available for systemic therapy. Mechanical debridement remains pivotal to this strategy because it not only significantly reduces the bioburden, but also opens a time-dependent therapeutic window for TAT (10).
This was a phase I/IIa, double-blinded, randomized, placebo-controlled two-part (Part A, Part B), multicenter study, including two centers, which primary objective was to determine the safety and tolerability of multiple doses of TP-102 in subjects with non-infected and infected DFU.

Methods

An Investigational New Drug (IND) application was submitted to the United States of America Food and Drug Administration and has been active since 1 October 2020 under No. 019670. Clinical trial approval by the institutional Helsinki committee, Ministry of Health and Medical Institution Director in Israel were granted on 06 Oct 2020, 11 Jan 2021 and 01 Feb 2021 respectively. The study was additionally approved by the Hadassah-Hebrew University Medical Center Ethics Committee.

Overall, the trial was a Phase I/IIa, double-blinded, randomized, placebo-controlled two-part (Part A, Part B), multicenter study, including two centers, to determine the safety and tolerability of multiple doses of TP-102 in subjects with uninfected and infected DFU. After signing the informed consent form, subjects were screened to assess their suitability to enter the study.

In Part A, 8 eligible subjects with uninfected DFU were enrolled within 7 days from screening (Cohort 1) and received IP three times weekly (TIW) every other day for up to one week. Upon completion of all subjects in Cohort 1, the cohort escalation committee (CEC) reviewed the safety data from all subjects and made a recommendation to the sponsor to proceed to Part B (Cohort 2).

In Part B, 18 subjects with a DFU with a grade 2 or 3 infection as per PEDIS classification and at least one bacterial isolate susceptible to TP-102, confirmed by culture of swab or biopsy collected from the target ulcer at screening visit, were included within 10 days from screening. Subjects received IP TIW every other day for up to four weeks and were randomized at a 2:1 randomization rate to either TP-102 or placebo.

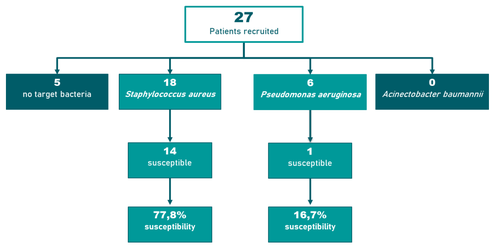
One mL of investigational product solution was applied topically per cm^3 of target ulcer. The titer of each bacteriophage in TP-102 was > $1x10^8$ to < $1x10^{10}$ PFU/mL. Assessments included safety and tolerability for all cohorts and efficacy for Cohort 2.

Results

- Cohort 1 ended on the 1st September 2021 with eight subjects with non-infected diabetic foot ulcers completing the study (Table 1).
- Recruitment to cohort 2 started 24th October 2021. In this cohort, to the end of study a total of 11 patients with infected diabetic foot ulcers were recruited (Table 2), one patient voluntary withdrawn from the study before initiating the treatment, remaining ten patients that finished the treatment (7 patients treated with TP102+ SoC and 3 patients with Placebo+SoC), while 9 finished the study due to one withdraw in the follow up visit. Due to slow recruitment of patients, Technophage decided to terminate earlier this phase I/IIa study in order to proceed to the next phases.
- On both cohorts, 18 subjects (male and female), 13 were known to be exposed to TP-102. The population characteristics in both TP-102+Soc and Placebo+Soc arms (Table 3) were similar, in terms of demographic and of subject characteristics at baseline.
- The wound characteristics in both TP-102+SoC and Placebo+SoC arms were also similar from baseline.
- In preliminary analysis:
  - Interestingly, 77,8% of S. *aureus* isolates from the wound were susceptible to TP-102 while only 16,7% of *P. aeruginosa* isolates were susceptible to the study phages. Overall, a variety of other bacteria, besides the target, were also isolated (Figure 1).
  - In few of the TP-102+SoC arm there was major reduction in the wound area and volume by the end of the study (Figure 2).
- No treatment emergent or treatment related adverse events related to TP-102 or placebo were reported during the trial in both cohorts.

Figure 1

Patients according to bacteria



Additional bacteria identified on patients' wounds

- *Klebsiella aerogenes*
- *Achromobacter xylosoxidans*
- *Streptococcus agalactiae*
- *Streptococcus dysgalactiae*
- *Streptococcus mitis*
- *Streptococcus oralis*
- *Citrobacter koseri*
- *Citobacter freundii*
- *Citrobacter braakii*
- *Finegoldia magna*
- *Staphylococcus haemolyticus*
- *Staphylococcus epidermidis*
- *Acinetobacter pittii*
- *Arcanobacterium haemolyticum*
- *Enterococcus faecalis*
- *Corynebacterium tuberculostearicum*
- *Escherichia coli*
- *Streptococcus spp. NOS*
- *Bacillus spp. NOS*

Table 1 - cohort I

Screen failure	2	
	TP-102	Control
Randomized	6	3
Withdrawn consent	0	1

Table 2 - cohort II

	TP-102	Control
Randomized	8	3
Withdrawn consent during study	1	0

Cohort II screen failures

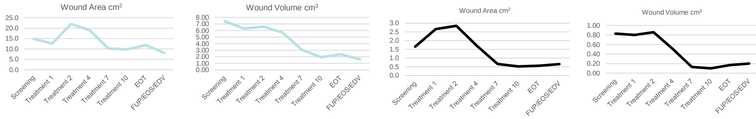
Total N= 16	
Bacteria non susceptible to TP-102	12
Infection too severe for study	3
Ulcer too deep	1
Low perfusion of foot	1
Fasciitis/osteomyelitis	2

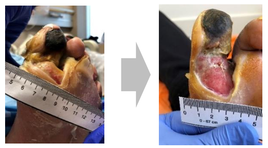
Table 3 - Patient characteristics in both cohorts

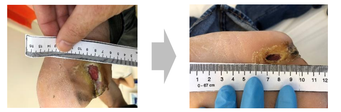
	TP-102 (N=13)	Placebo (N=5)
Age mean (sd)	59.5 (11.8)	55.8 (11.26)
Male/Female	11/2	1/1
Weight, Kg mean (sd)	92.7 (18.3)	99.4 (17.6)
BMI mean (sd)	30.7 (4.6)	32.4 (6.5)
NIDDM	13	5
Duration of NIDDM – years mean (sd)	19.9 (11.3)	12.2 (10.1)
Insulin treatment	10	5
Other assocaited diseases Number out of the cohort		
Renal impairment	5	0
HTN	12	4
Cardiac disease	4	0
PVD	8	2
Rethinopathy	8	2
Dyslipidemia	12	4
Amputation	7	3

Figure 2

Two representation of local treatment response over time with TP-102







Conclusions

- Globally, the safety and tolerability of TP-102 following topical administration of multiple doses to diabetic patients with uninfected and infected diabetic foot ulcers was confirmed.
- Preliminary data suggests that innovative bacteriophage therapy TP-102 is effective in reduction of diabetic foot ulcers volume.
- *S. aureus* strains isolated from the patients wounds were highly susceptible to the investigational product.
- The next phases for evaluation of the product are already being prepared and are planned to start in the next year.

References

1. BioMedGPS. Smart TRAK February 2012 Market Analysis 2012
2. Boulton AJ. Diabetes Metab Res Rev. 2000;16 Suppl 1:S2-5.
3. Boulton AJ. Diabetologia. 2004;47(8):1343-53.
4. Frykberg RG, Zgonis T, et al. J Foot Ankle Surg. 2006;45(5 Suppl):S1-66.
5. Andrews KL, Houdek MT, Prosthet Orthot Int. 2015;39(1):29-39.
6. Lipsky BA, Hoey C. Clin Infect Dis. 2009;49(10):1541-9.
7. Mendes JJ, Marques-Costa A, et al. Diabetes Res Clin Pract. 2012;95(1):153-61.
8. Lam PL, Lee KKH, et al. Crit Rev Microbiol. 2018;44(1):40-78.
9. Mendes J, Neves J. J Diab Foot Complic. 2012;4(2):26-45.
10. Wolcott RD, Rumbaugh KP, et al. J Wound Care. 2010;19(8):320-8.

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Authors: D. Jones-Dias[3] S. Gonçalves[3], M. Barreto[3] were added to the poster after the initial submission to reflect there contribution the data currently presented in the poster.

The Cohort II included also patients recruited in the Ichilov-Tel Aviv Medical Center Lead by Prof. Ronen Ben-Ami and Dr. Michal Dekel.