Preliminary safety and efficacy 12 weeks results of PhagoDAIR-I, a Pilot Study of Phage Therapy in Patients with Hip or Knee Prosthetic Joint Infection due to *Staphylococcus aureus*.

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Introduction:

- Bacteriophages are natural viruses that specifically infiltrate bacterial cells, disrupting their metabolism, and causing bacterial lysis
- Prosthetic joint infections (PJI) of the hip or the knee, particularly when caused by *Staphylococcus aureus* are still difficult to treat
- *S. aureus* PJI is associated with significant morbidity, mortality (five years mortality of 25%) and high economic burden
- DAIR (Debridement, Antibiotics and implant Retention) is frequently used as conservative approach, particularly when infection occurs in the first weeks after prosthesis implant, with variable efficacy, in the range of 55-65%
- Phage therapy, with its positive impact on biofilm, could significantly improve the outcome of DAIR and PJI
- We report here the 12 weeks results of PhagoDAIR, a pilot study of phage therapy in patients with hip of knee PJI with an indication for DAIR and suppressive antibiotherapy

Methods:

PhagoDAIR-I is a pilot, randomized, non-comparative double-blind study. Patients with hip or knee PJI due to *S. aureus* with an indication for late DAIR (> 1 month after prosthesis implant) and suppressive antibiotherapy were randomized in a double-blind manner to DAIR + phages or DAIR + placebo (*Figure 1*).

Patients are treated by intra-articular injection with 2 phages (PP1493 and PP1815) or placebo (Sodium Chloride 0.9%). Administration is taking place either during DAIR or by ultrasound guidance 2 weeks after DAIR.

All patients receive curative antibiotherapy for 12 weeks followed by suppressive antibiotherapy. Patients are followed between 1 and 2 years.

The primary endpoint is the rate of clinical control at 12 weeks. Patients without control of the *S. aureus* infection can receive salvage therapy with both phages administered by ultrasound guidance once a week for three consecutive weeks.

Figure 1 : PhagoDAIR study design

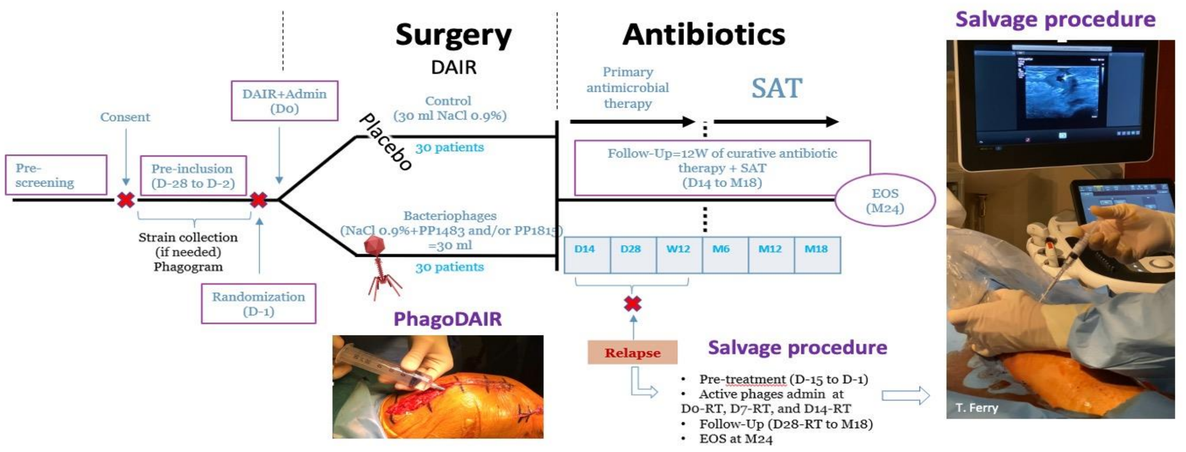


Table 1: Patients characteristics - Efficacy population

		Statistics	Overall N=26	Bacteriophages arm N=19	Control arm N=7
Age (in years)	-	N (N missing)	26 (0)	19 (0)	7 (0)
		Mean (SD)	64.9 (±16.75)	66.1 (±16.40)	61.6 (±18.56)
		Median (Q1 ; Q3)	68.5 (52.0;79.0)	69.0 (52.0;83.0)	68.0 (41.0;79.0)
		Min ; Max	(27.0;85.0)	(27.0;85.0)	(39.0;80.0)
Gender	Male	n/M (%)	16 (61.5%)	10 (52.6%)	6 (85.7%)
	Female	n/M (%)	10 (38.5%)	9 (47.4%)	1 (14.3%)

Table 2: Rate of relapse at Week 12

Modality	Statistics	Overall N=26	Bacteriophages arm N=19	Control arm N=7
Relapse of Infection	n/M (%) [95% CI]	7 (26.9%) [13.7;46.1]	5 (26.3%) [11.8;48.8]	2 (28.6%) [8.2;64.1]
No Relapse of Infection	n/M (%) [95% CI]	19 (73.1%) [53.9;86.3]	**14 (73.7%)** [51.2;88.2]	5 (71.4%) [35.9;91.8]

Table 3: Adverse events up to week 12. Safety population

	Overall N=29		Bacteriophages arm N=20		Control arm N=9	
Adverse events (AE)	Nb AEs (%)	Nb patients (%)	Nb AEs (%)	Nb patients (%)	Nb AEs (%)	Nb patients (%)
All AEs	182 (100.0%)	29 (100.0%)	104 (100.0%)	20 (100.0%)	78 (100.0%)	9 (100.0%)
Non-Treatment Emergent AEs (NTEAE)	22 (12.1%)	11 (37.9%)	14 (13.5%)	5 (25.0%)	8 (10.3%)	6 (66.7%)
Treatment Emergent AEs (TEAE)	160 (87.9%)	29 (100.0%)	90 (86.5%)	20 (100.0%)	70 (89.7%)	9 (100.0%)
AE post rescue treatment	15 (8.2%)	4 (13.8%)	13 (12.5%)	3 (15.0%)	2 (2.6%)	1 (11.1%)
Mild TEAEs	72 (39.6%)	24 (82.8%)	44 (42.3%)	16 (80.0%)	28 (35.9%)	8 (88.9%)
Moderate TEAEs	61 (33.5%)	19 (65.5%)	32 (30.8%)	12 (60.0%)	29 (37.2%)	7 (77.8%)
Severe TEAEs	22 (12.1%)	15 (51.7%)	12 (11.5%)	10 (50.0%)	10 (12.8%)	5 (55.6%)
Serious TEAEs	17 (9.3%)	12 (41.4%)	9 (8.7%)	6 (30.0%)	8 (10.3%)	6 (66.7%)
Related TEAEs	2 (1.1%)	1 (3.4%)	2 (1.9%)	1 (5.0%)	0 (0.0%)	0 (0.0%)
Serious related TEAEs	2 (1.1%)	1 (3.4%)	2 (1.9%)	1 (5.0%)	0 (0.0%)	0 (0.0%)

Results:

Due to difficulties with recruitment, only 29 patients were randomized, all in France. Efficacy analysis was performed on 26 patients (19 on phages and 7 on placebo, *Figure 2*). Safety analysis was performed on 29 patients (20 on phages and 9 on placebo). Stratification by center and prosthesis location, associated with few patients recruited per site led to this important unbalance.

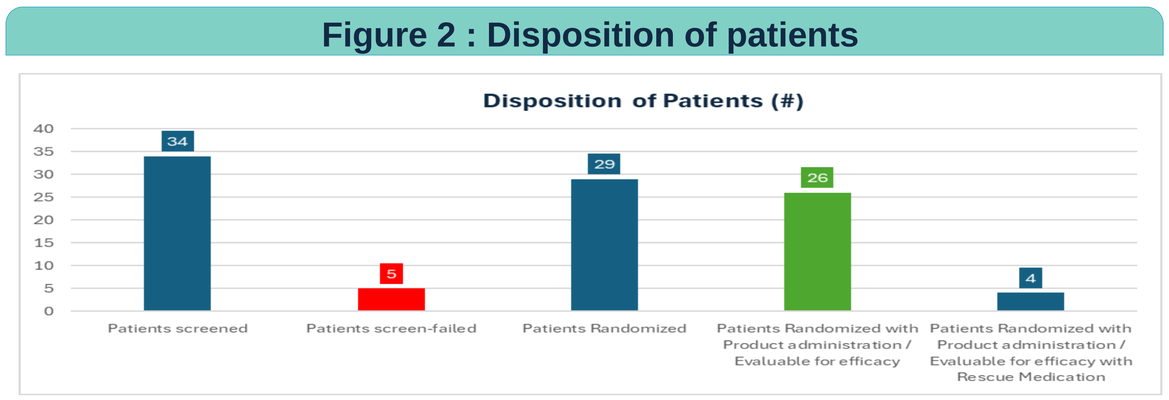
Patients' characteristics are presented in *Table 1*. While gender was well distributed in the phage arm, only one woman was included in the placebo arm.

The rate of clinical control was 14/19 (73,7%) in the phage group and 5/7 (71,4%) in the placebo group. Out of the 7 patients who relapsed up to week 12, 5/19 relapsed in the phage arm and 2/7 in the placebo arm (*Table 2*).

The salvage procedure was activated for 4 out of the 7 patients without control of infection (one received placebo at baseline) leading to disease control without any sign of infection 12 weeks after its activation in 2 patients **(overall control with phages: 16/20= 80%).**

No safety issue was identified (*Table 3*).

Figure 2 : Disposition of patients



Conclusion:

From the 29 patients randomised, 26 were evaluable for efficacy analysis. Due to a major inbalance between the 2 groups (19 in the phage arm and only 7 in the placebo arm), the analysis of the efficacy data in the placebo group is problematic. **The rate of clinical control at 12 weeks in the phage arm is of 74%.** Considering patients treated with salvage therapy, the **overall rate of success with phage therapy administered between one to three times on a weekly basis is 80% (16 out of 20)**. Phage therapy was well tolerated.

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