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# EXPERIENCE FROM ONGOING PHAGOBURN CLINICAL TRIAL

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EUROPEAN MEDICINES AGENCY  
WORKSHOP THERAPEUTIC USE OF BACTERIOPHAGES  
8 JUNE 2015



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# DISCLOSURE

» None



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# PLAN

1. Background
2. Clinical study
3. Adjustments



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# OUR MEDICAL OBJECTIVES

- » Main objective: Proof of concept
  - » Use of phages in human bacterial infections

PubMed (Mesh):

Bacteriophages= 51 662 references

Bacteriophages/ therapeutic use = 20 references

- » Secondary objectives
  - » Causes of failure
  - » Evolution of local flora
  - » Healing improvement



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# OTHER OBJECTIVES

- » Interaction with antibiotics
- » MRD bacteria

131 referenced publications in the last 5 years

- » Modulation of immune response
- » Impact on gut flora

Brüssow, 2005 Microbiology

Sarker 2012, Virology

- » Bio distribution: absorption, clearance, elimination...

***In only 36 months***



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# CHOICE 1: BURN UNITS

- » Topical application: [BMJ, 1970](#)
  - » IV is more complicated
  - » Topical application instead of antibiotics
  - » numerous adverse effects with topics currently used
- » Strong policy about use of antibiotics
- » Skilled environment: Medical, nurses...

To be successful the dressings must be well soaked with the phage. Quite a lot of this filtrate is needed, but this presents no problems to the bacteriologist. If more than one organism is isolated separate phages will be needed, usually two or three at most, mixed roughly in the proportion they appeared in the original cultures and films.

The results in the patient referred to were quite dramatic. The picture changed rapidly from that of an indolent, unprogressive septic state to a clean, healthy healing surface. This form of treatment is also very effective in severe carbuncles and boils.—I am, etc.,

GEOFFREY SHERA.

Eastbourne, Sussex.





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# CHOICE 2: 2 BACTERIA

» *E coli:*

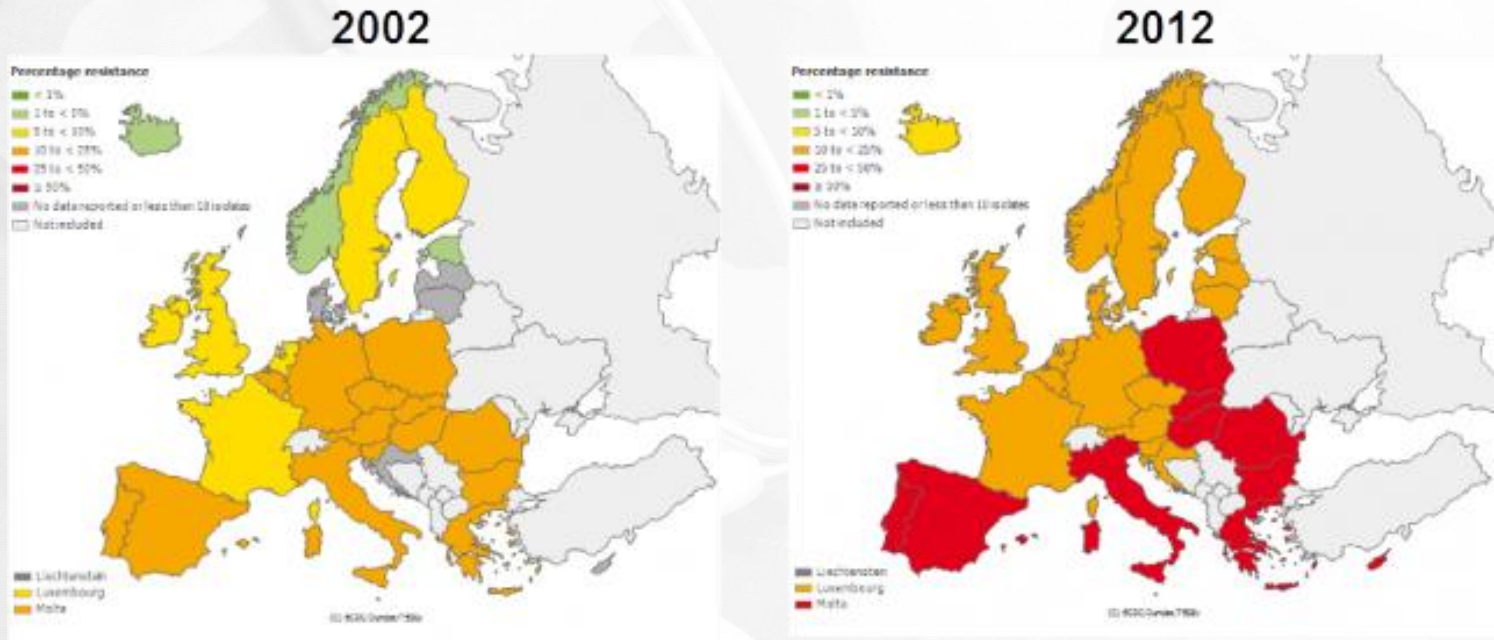
» in charge of 60% of burned skin infection

» Many published data on phages Vs *E.coli*

» *P aeruginosa:*

» *One the most difficult strain to cure*





Comparative proportion of fluoroquinolones resistant *Escherichia coli* isolates in EU during the last ten years. | Credit: European Centre for Disease Prevention and Control (ECDC).





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# CHOICE 3: COCKTAILS

- » Reduce risk of failure +++
- » Reduce risk of emergence of phage resistant strains
- » Natural Vs modified lytic phages: regulatory tolerance
- » Pre-clinical tests available (efficacy and safety)





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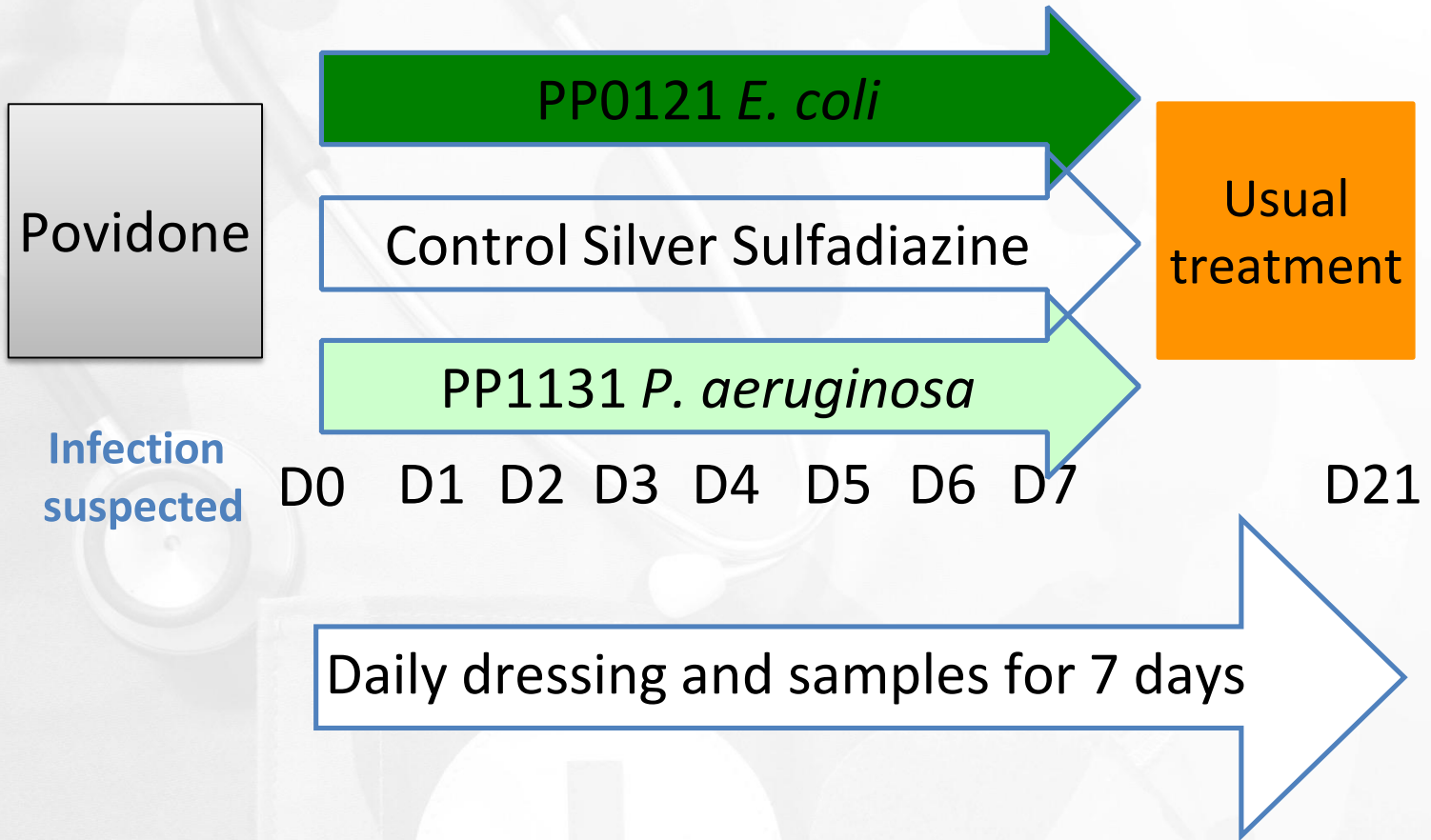
# ORGANIZATION

- » International
- » Multi centric study
- » *In-hospital* patients
- » Critical care environment
- » Cooperation with regulatory agencies:
  - » French / Swiss / Belgian / EMA
- » Respect of good medical practices
- » Standardization of care +++

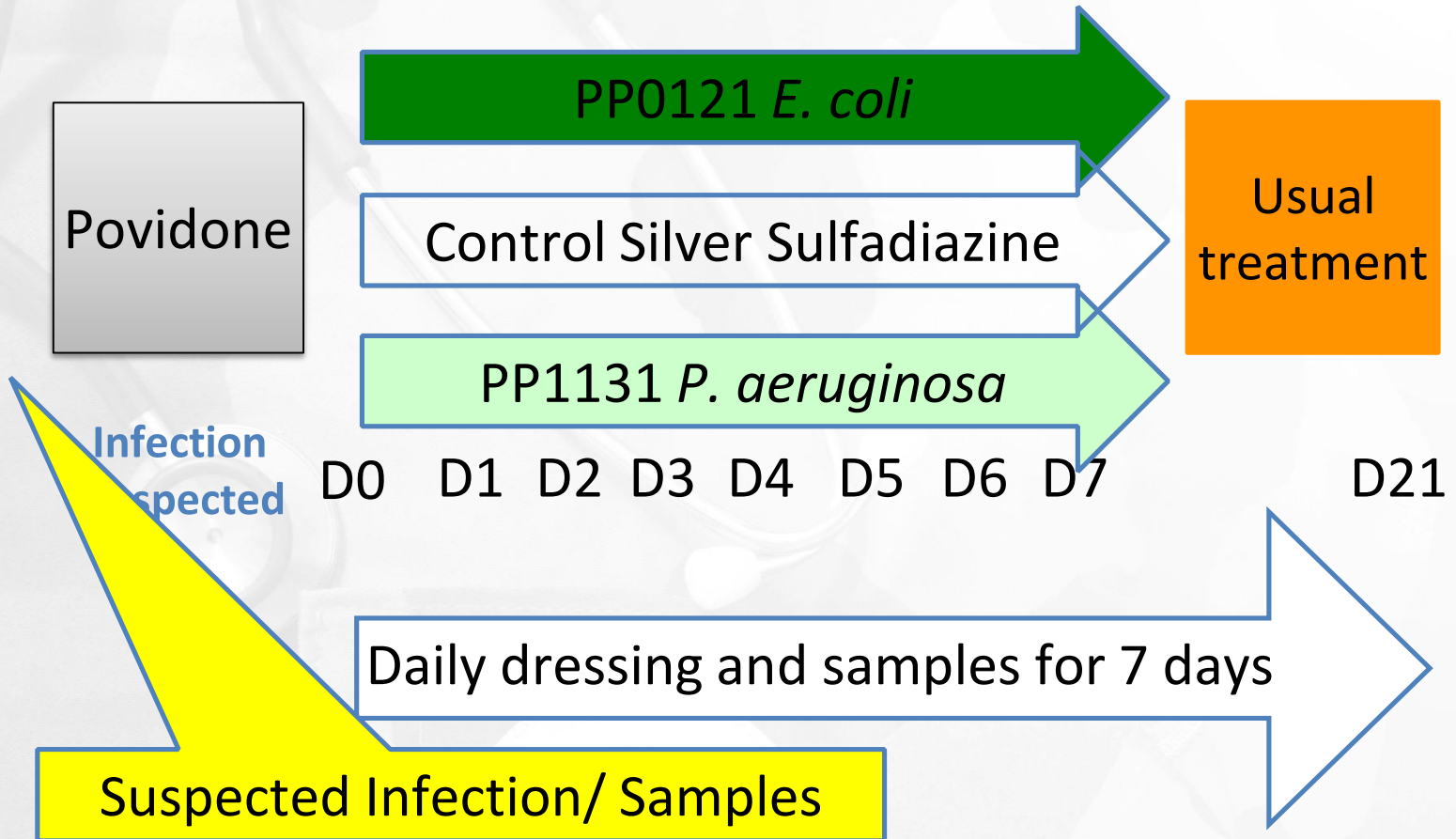


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# DESIGN



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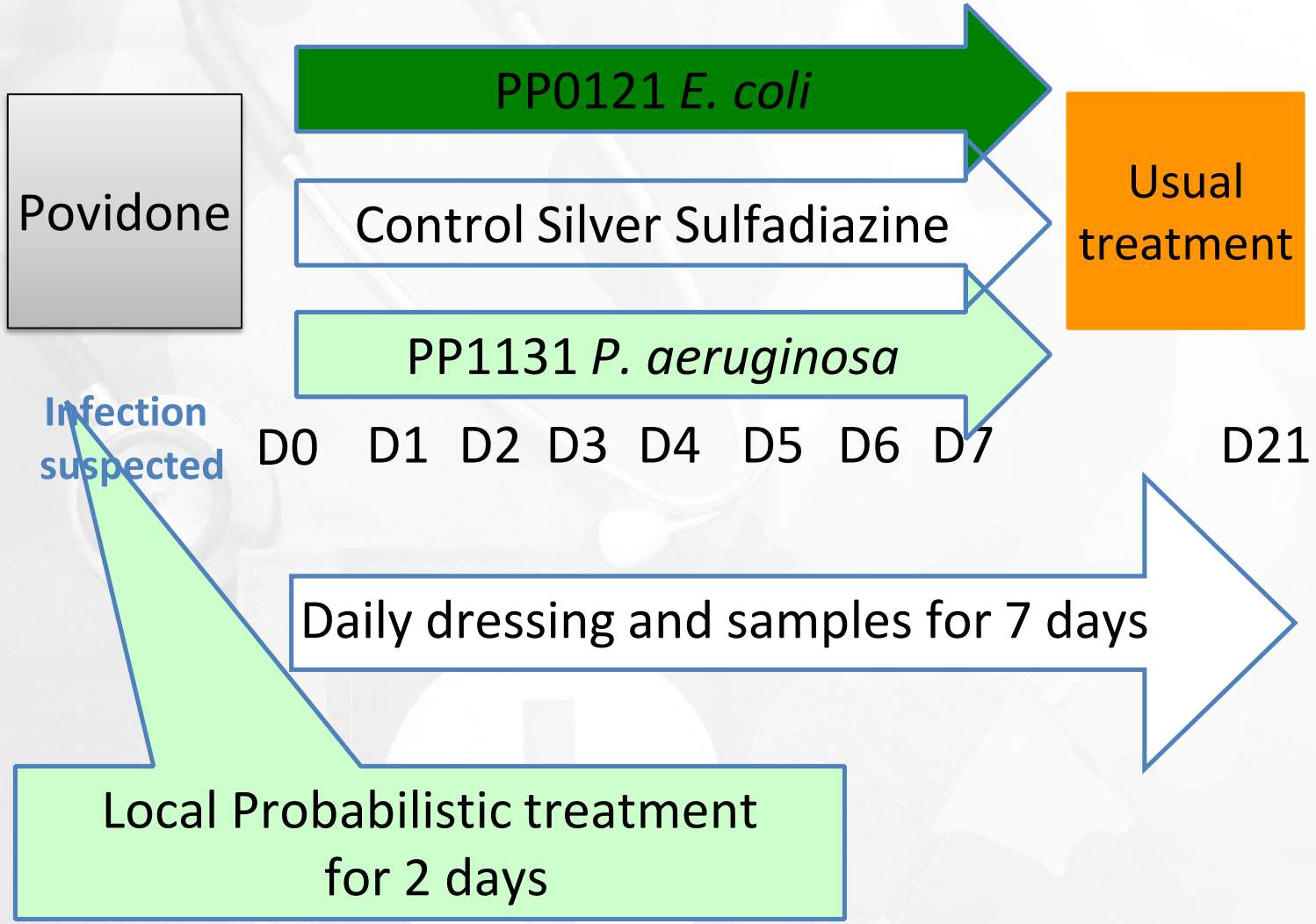
# CLINICAL CRITERIA OF INFECTION

- » Local or loco-regional inflammatory reaction
- » Adverse or Unexpected local evolution
- » Purulent wound
- » Fast debridement or delayed healing of donor site
- » Blackish spot
- » Conversion of superficial wound in a deeper wound

*SFETB, guidelines*



# DESIGN





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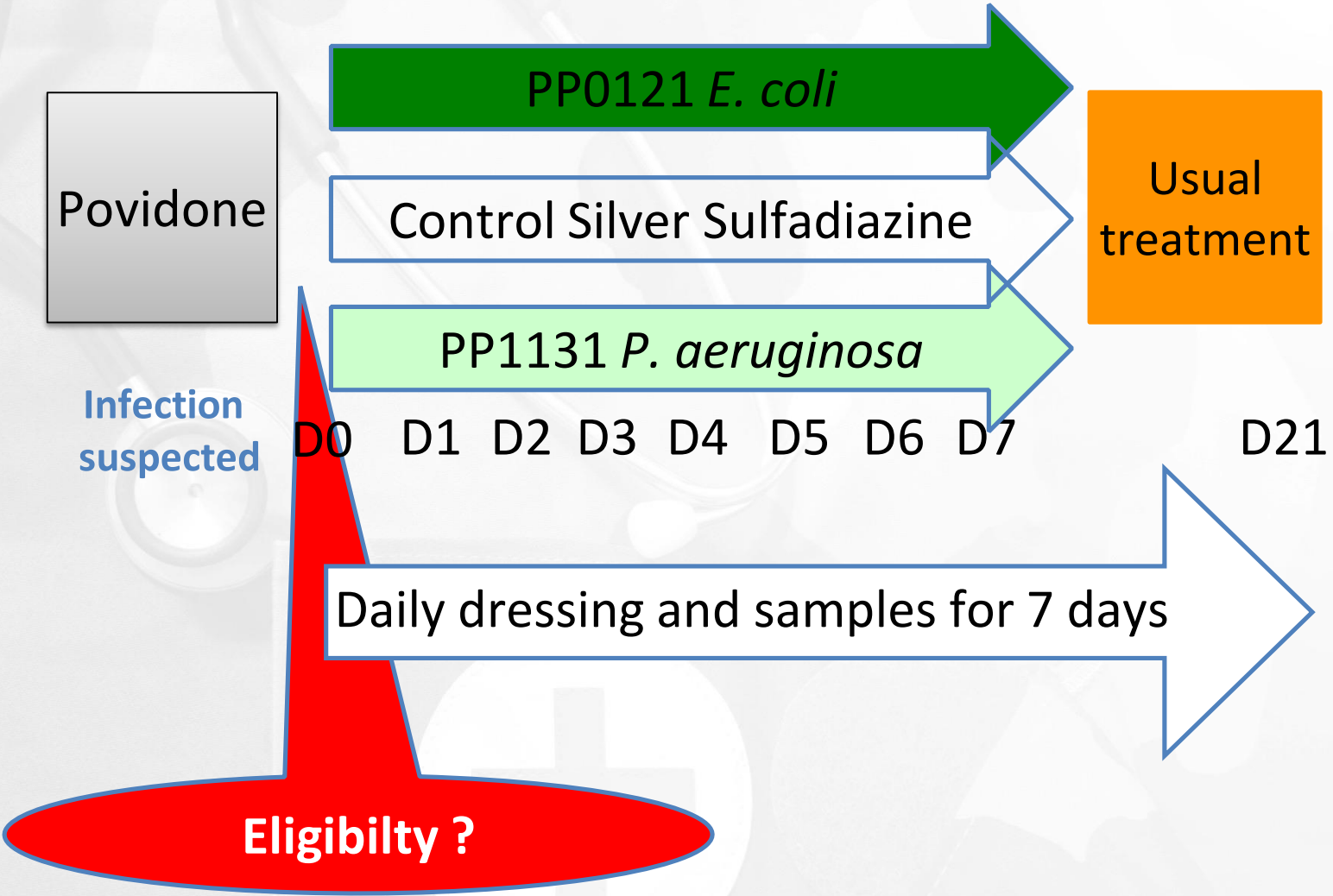
# POVIDONE IODINE

- » Usual probabilistic topical treatment
- » Pathogen none yet identified: Cocci Plus Vs Gram Negative Bacillus
- » Adverse effects / restriction of use
- » No negative interaction with phages



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# INCLUSION CRITERIONS

- » Man or woman
- » Adult
- » Informed consent obtained
- » In-hospital patient in a burn unit
- » Infected wound: SFETB standards
- » *E coli* or *Pseudomonas aeruginosa*, whatever antimicrobial resistance



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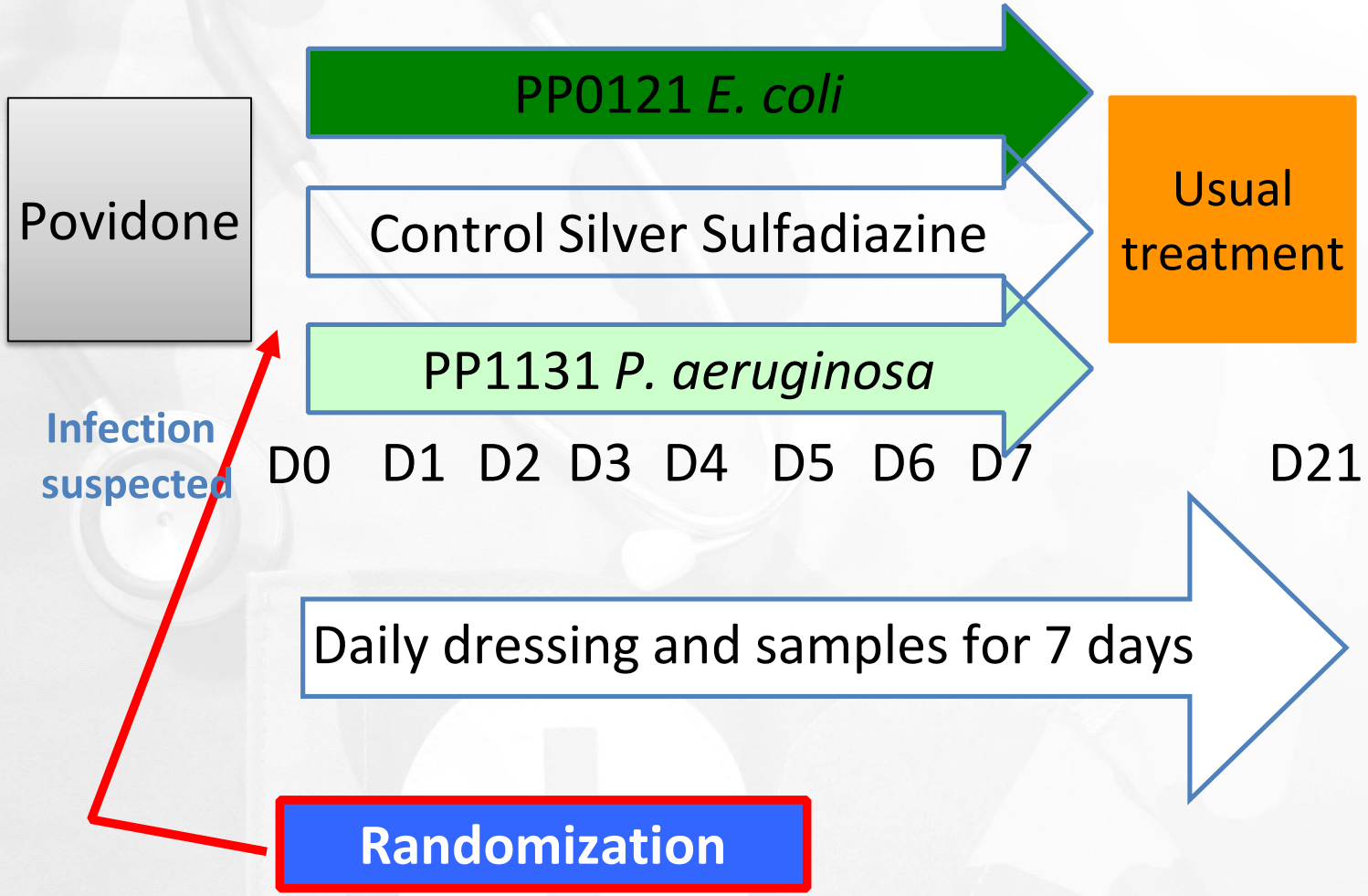


# EXCLUSION CRITERIA

- » Child under 18
- » Pregnant or breastfeeding woman
- » Undercurrent condition requiring a treatment which may interfere with analysis results: such as high dose of chronic corticotherapy, immunosuppressive medication, oncologic chemotherapy
- » Patient included in an interventional research protocol with therapeutic intervention still ongoing upon inclusion time or having participated into anti-infective drug trials during the previous month. Patient previously included in the study
- » Vulnerable population
- » Patient for whom treatment limitation or withdrawal during study period is considered
- » *General or local Known sensitization to sulfamides*



# DESIGN



# PP0121 AND PP1131



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- **PP0121**: Mix of 13 lytic phages lytiques against *Escherichia coli*
- **PP1131**: Mix of 12 lytic phages lytiques against *Pseudomonas aeruginosa*

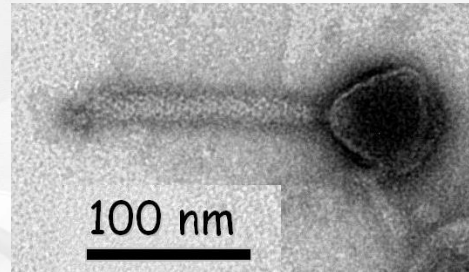


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# CHARACTERIZATION

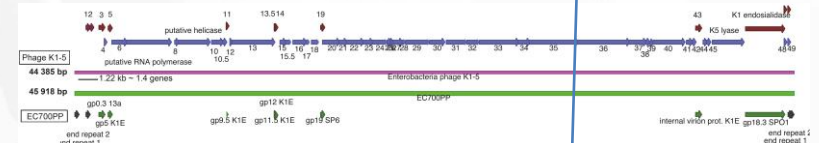
Action profile

	Phage PYO	1433
1	LMG 24882	+
2	LMG 24883	+
3	LMG 24886	+
4	LMG 24887	+
5	LMG 24891	+
6	LMG 24892	+
7	LMG 24893	+
8	LMG 24895	
9	LMG 24896	+
10	LMG 24898	+
11	LMG 24901	
12	LMG 24903	+/-
13	LMG 24904	+/-
14	LMG 24905	+
15	LMG 24907	
16	LMG 24909	+
17	LMG 24913	+/-
18	LMG 24914	
19	LMG 24916	+
20	LMG 24918	



Classification :  
**Ordre : Caudoviridae**  
**Family : Myoviridae**  
**Gender : PB1/KPP12-like**

Morphotypage

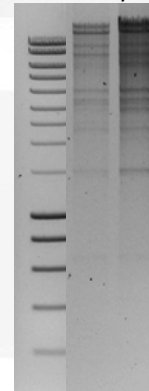


Genomic Sequencing

Genomic analysis

- 66 212 pairs of bases
- Genre PB1/KPP12-like Lytic phage
- No toxin gen
- No integrase

Integrity tests



# PRE CLINICAL SUMMARY

	Cocktail anti COLI		Cocktail anti PYO	
	mice	Mini-pigs	mice	Mini-pigs
Characterization of $\phi$		✓		✓
Efficacy SC, IP, IV	✓		✓	
Innocuousness SC, IP, IV	✓		✓	
PD via SC, IP, IV	✓		✓	
Doses	✓		✓	
Cutaneous tolerance		✓		✓
Innocuousness IV		✓		✓
PD via IV		✓		✓

STATUT PRODUITS

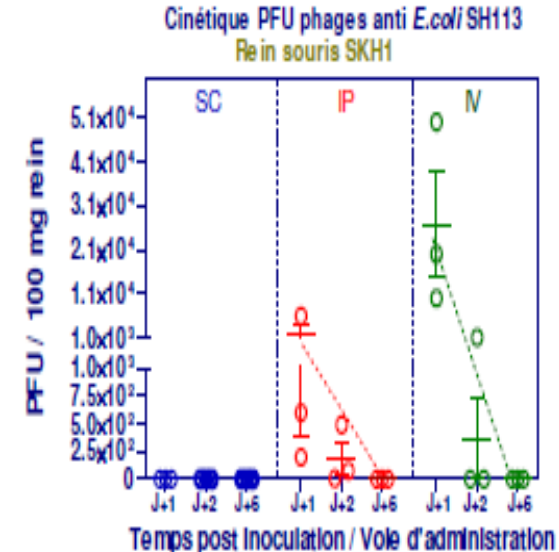
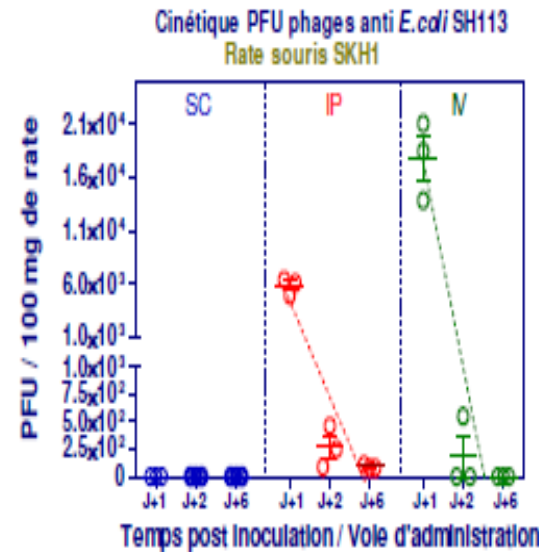
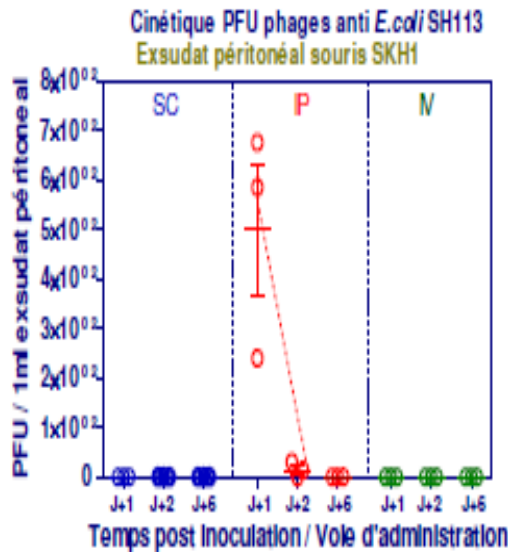
# PK OF PP0121



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Injection of 100 $\mu$ l of cocktail at 10<sup>8</sup> PFU



With PP1131, identical results were observed





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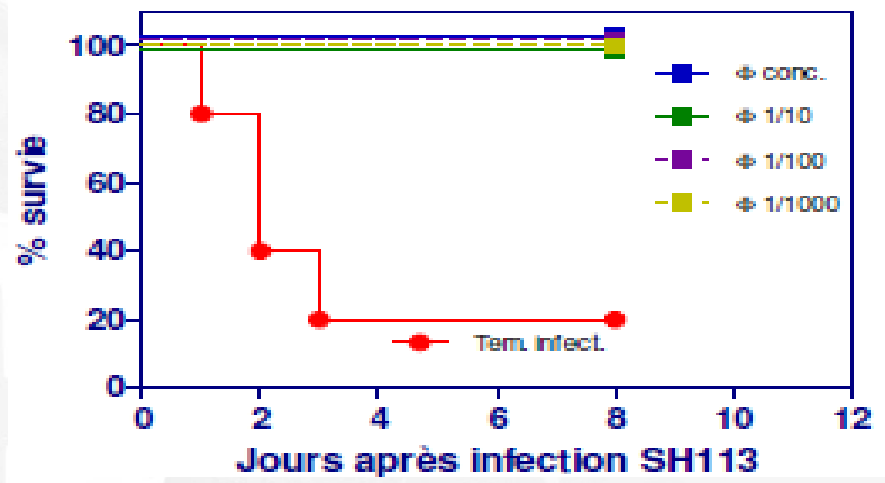
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# BURNED INFECTED IMMUNOSUPPRESSED MICE

Jour	-3	-2	-1	0	1	2	3	4
	1,5mg Cy	Burn	1,5mg Cy	Infection	1,5mg Cy			
Mode injection	IP	Yperite	IP	SC 10 <sup>7</sup> cfu	IP			
PHAGE				SC 6h post-infection				

- Conclusions PP0121**
- No treatment Survival rate : 20%
  - Treated J0 (infection+6h) via SC :SR = 100%
  - Dilution of cocktail from 10<sup>8</sup> to 10<sup>5</sup> PFU/ml

Souris SKH1 (Cy/Yp) infectées SC par *E. coli* SH113 traitées par cocktail  $\Phi$  anti-*E. coli*







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# CONTROL GROUP

- » Silver sulfadiazine
- » Broad spectrum antiseptic activity
- » Instead of :
  - Sulfamylon<sup>®</sup>: Temporary use
  - Colimycin preparation : Local preparation
  - Hypochlorite Bath
- » Expert agreement
- » Several Known adverse effects



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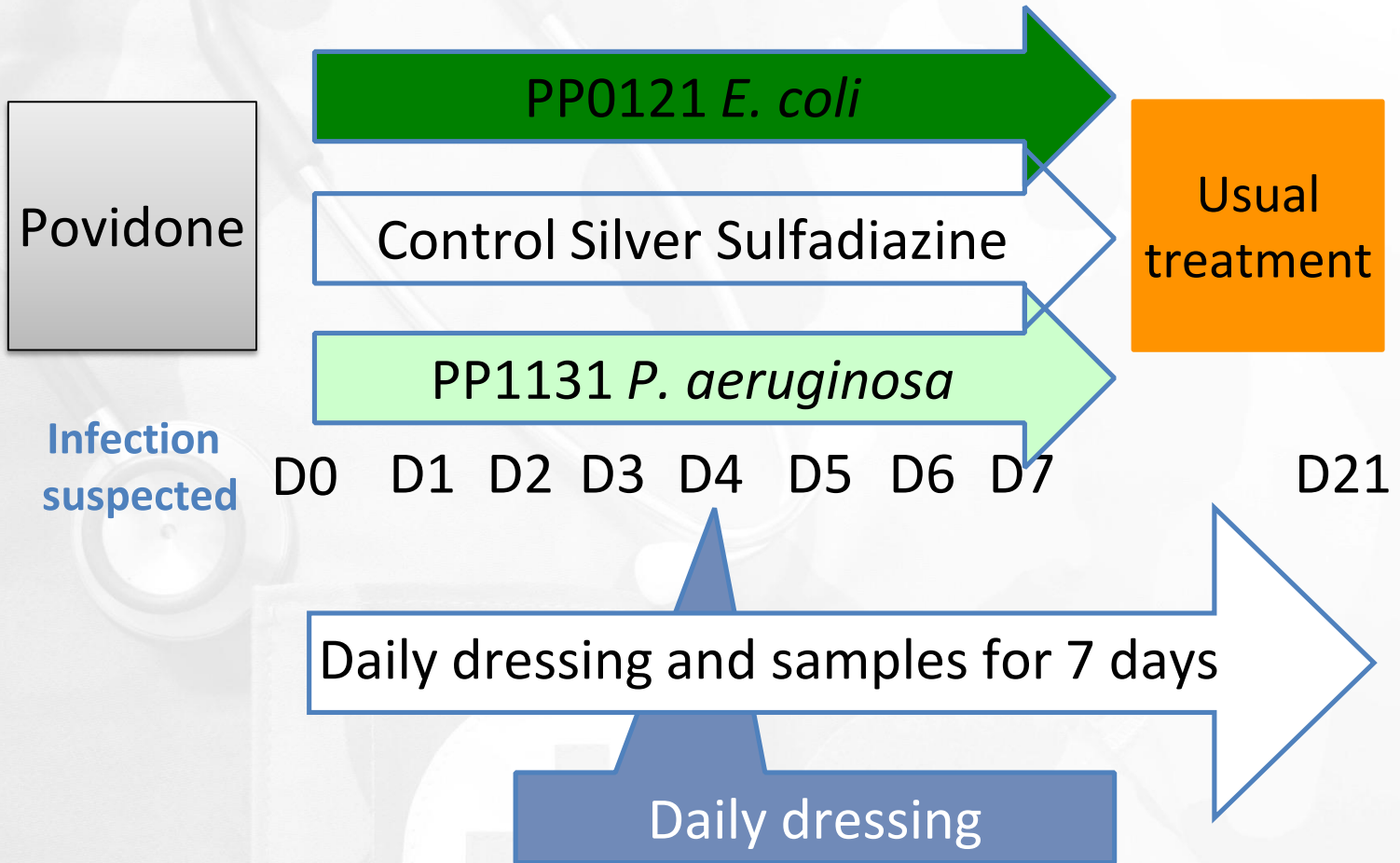


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# SUMMARY

Study procedure	V0 D0	V1 D1	V2 D2	V3 D3	V4 D4	V5 D5	V6 D6	V7 End of treatment D7	V8 D14	V9 End of study D21
Informed consent	X									
Demography / baseline	X									
Verification of inclusion/non- inclusion criteria	X									
Clinical exam of the wound	X	X	X	X	X	X	X	X		
Bacteriological sample	X	X	X	X	X	X	X	X		
Blood samples	X			X		X		X	X	X
Burn wound inspection	X	X	X	X	X	X	X	X		
Treatment (phage cocktails or silver sulfadiazine)	X	X	X	X	X	X	X	X		
Collection of local, regional and general tolerance criteria	X	X	X	X	X	X	X	X		
Concomitant pathologies/ Concomitant medications	X	X	X	X	X	X	X	X		
AEs report	X	X	X	X	X	X	X	X	X	X





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# ADJUSTMENTS

» Increase duration of study

36 months

» Increase number of investigation sites

11 centers

NNT = 220 patients / 1 year

» Adjustment in cocktail use to reduce workload of teams and errors in re-composition



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# REGULATORY DISCUSSIONS

- » Management of adverse effects:
  - » control group: Silver Sulfadiazine
  - » study group: GRAS (Generally Recognized As Safe)
- » Interactions with ongoing antibiotics
  - » With or without effect on the treated strain
- » Education and information of teams



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# NEXT DEVELOPMENTS

- » First inclusion expected before 1<sup>st</sup> July
- » DSMB every 3 months, 50 patients
- » Open data to agencies
- » Specific management of potential adverse effects
- » Non blind for investigator, so inclusions would be easy whether clinical results are positive
- » Results will be known in 1 year





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# WHAT HAVE WE LEARNT ?

- » Many questions to answer in a single study: efficacy, safety, metabolism...
- » *In vivo/vitro*, Animal/human differences
- » Collaborative work with many different components





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# CONCLUSIONS

- » PHAGOBURN is the first multi centric clinical study ever done on human phage therapy
- » Whatever the results, after PHAGOBURN further studies will be necessary
- » It's now time to move from a belief to scientific evidence

