European Federation of Pharmaceutical Industries and Associations

Development of Drugs for Eradication of Nasal Carriage of *S. aureus* to Reduce *S. aureus* Infections in Vulnerable Surgical Patients

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Agenda for this talk

- Context
  - Importance of carriage
  - Challenge of clinical trials
  - Possible label wording
- Ways to go forward
  - What is eradication?
  - What is the impact of eradication?
  - Next steps?

Eradication of carriage

- Nasal/gut colonization with pathogens is common
  - *S. aureus, N. meningitidis, H. pylori, C. difficile,* gut flora (selective decontamination), MDR Pathogens
  - Logically, you can't get infected if the pathogen is not present
- There are precedents for this concept
  - nasal mupirocin: *S. aureus*/MRSA/MSSA
  - oral ciprofloxacin/rifampicin: *N. meningitidis*
  - oral clarithromycin/amoxicillin/metronidazole: *H. pylori*
- Regulatory focus going forward on proven clinical benefit over and above successful eradication (draft guideline 4.2.1.5.4)
- Focus for this talk: *S. aureus* decolonization

S. aureus nasal eradication

- Premise: *S. aureus* nasal carriage is an important risk factor for infection due to *S. aureus*[1,2] in high risk patients
- Control of MRSA/MSSA remains a challenge
  - Mupirocin resistance is rising
- New agents are needed:
  - How can we achieve this?
  - Trials based on clinical endpoints are not possible (next slide)…

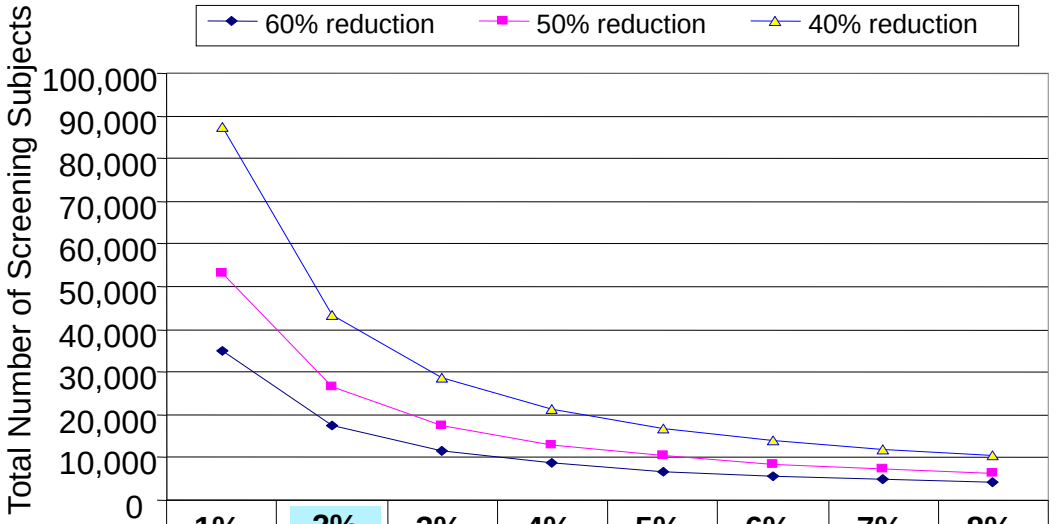
1. Munoz *et al*. J Hosp Inf 2008; 68: 25-31
2. Kluytmans *et al*. Infection 2005; 33: 3-8

Context

S. aureus nasal eradication: Sample sizes for a trial powered on clinical benefit are in the thousands

Scenario:
- 25% screened = nasal *S.aureus* carriers
- 2% placebo infection rate post-op
- objective: 50% reduction of infections
- 90% power, two-sided type-1 error 5%

→ 26,400 subjects required to show 50% event reduction



	1%	2%	3%	4%	5%	6%	7%	8%
60% reduction	35,064	17,408	11,528	8,584	6,816	5,640	4,800	4,168
50% reduction	53,200	26,400	17,472	13,008	10,328	8,544	7,264	6,304
40% reduction	87,328	43,320	28,656	21,320	16,920	13,984	11,888	10,320

Post-surgery infection rate in placebo group

Slide from EFPIA presentation at Feb 2011 EMA guidance workshop

Labelling as a view to the problem

- But, the point of any such product is to prevent infection
- So, how do we go from this…
  - Bactroban nasal is indicated for the eradication of nasal colonisation with MRSA in adult patients and health care workers as part of a comprehensive infection control programme to reduce the risk of infection among people in high risk of MRSA infection during institutional outbreaks of infections with this pathogen.
- To this?
  - Product X is indicated for the eradication of nasal colonisation with staphylococci including MRSA to reduce the risk of post operative staphyloccal infections in high risk patients.

What is eradication?

- The possible tools are well known
  - Culture, PCR, etc
- Can we work together to validate some measure of microbiological eradication as reliable predictor of clinical benefit?
  - Review previous successful papers and micro methodologies and agree microbiological methods
  - Focus on tools that offer high face validity, long track records, and wide-spread availability
  - Also think through issues of measurement timing / duration

What is the impact of eradication?

- Logically, there must be an impact
  - If the organism is eradicated, endogenous infection is not possible
- How do we decide?
  - Collective review of available data
  - Workshop-based discussion and analysis
- Goals of this work
  - Summarize and agree interpretation of available data
  - Where needed, generate plans for additional research
  - Also identify possible negative effects of decolonization
- In so doing, create a road-map for development

Next Steps

- New agents for *S. aureus* decolonization are needed
- Eradication logically should offer value
  - Need to define methods and value.
- Existing data are probably adequate to show that value
- We would like to find a way to create a public conversation on this that enables future work