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\textsuperscript{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)…

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

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*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