Potent *in vivo* efficacy demonstrated for epidermicin NI01 in an MRSA wound infection model

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In the UK, over 10% of antibiotic prescriptions are for skin infections. New therapeutic approaches are required to treat and prevent such infections, and new modalities may be favourable. Epidermicin NI01 is a first-in-class bacteriocin with potent activity and a novel mode of action against MRSA and Streptococci, leading causes of community and healthcare acquired skin infections and a significant burden of antimicrobial resistance (AMR). NI01 has single dose efficacy in a mouse model of nasal decolonisation. We now present evidence that NI01 has potent efficacy in a robust model of MRSA skin infection in mice, with activity comparable to that of standard of care agents for treatment of impetigo (NICE guidelines).

Male CD1 mice (Charles River Labs; n=6 per treatment group) were immunosuppressed with cyclophosphamide, (150 mg/kg and 100 mg/kg on days -4 and -1, respectively). Dorsal skin (1 x 2 cm) was shaved, and hair removed before skin tape-stripping 3 times and topical application (10 µL; 2 x 10^6 cfu/mouse) of *S. aureus* strain USA300. Topical q24h administration of 50 µL of vehicle (0.5% HMPC) or NI01 (4 dosing regimens in 0.5% HPMC) or 50 mg of Bactroban 2% (mupirocin) or Fucidin 2% (fusidic acid) was initiated at 24 hours post-infection (hpi). Weight monitoring, general health assessment and skin clinical scoring was conducted daily until the endpoint at 96hrs when infected skin was recovered for quantitative skin burden (cfu/g) analysis.

There was no marked weight loss in any groups and mice did not exhibit any general signs of illness or adverse effects due to infection or treatment. No efficacy was seen in the 3% NI01 mono-dose group (See Table). Treatments resulted in significant Log_{10} reductions in cfu/g tissue of 2.82 (Fucidin), 2.48 (3% NI01 q24) and 2.47 (Bactroban). The MIC of NI01 for *S. aureus* strain USA300 was 4µg/ml before the study and *ex-vivo*.

These data warrant further development of NI01 for use in topical therapy of infections caused by priority pathogens and validates expansion of our AI-driven discovery pipeline for drugs in the epidermicin class. Clinical use would spare conventional antibiotics for serious and systemic infections.

Treatment group	Endpoint (hpi)	Mean weight change (%)	General clinical score	Average skin score	Group geo mean (cfu/g)*	Log_{10} geo mean (cfu/g)	Log_{10} difference from vehicle (cfu/g)	Log_{10} std dev (cfu/g)
Vehicle	96	0	1	2	4.64×10^6	6.45	**N/A**	1.91
NI01 0.5%, q24h	96	2.3	1	2	3.07×10^5	5.31	**1.14**	1.60
NI01 1%, q24h	96	0	1	2	8.69×10^5	5.87	**0.58**	1.02
NI01 3%, q24h	96	0	1	2	1.38×10^4	3.97	**2.48**	1.28
NI01 3%, once	96	1.6	1	2	1.40×10^7	6.95	**-0.5**	1.78
Bactroban 2%, q24h	96	0	1	1	1.15×10^4	3.98	**2.47**	0.94
Fucidin 2%, q24h	96	1.3	1	2	4.94×10^3	3.63	**2.82**	0.73

*The LoD was 2.11 log10 cfu/g. Statistical analysis was conducted by way of Ordinary one-way ANOVA on log-transformed data followed by Tukey's multiple comparisons test using Graphpad Prism 10.4.0