A Pilot Study to Evaluate the Safety and Efficacy of NVC-422 Topical Gel in Impetigo, Including MRSA

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♦ Abstract

Background. Impetigo is a highly contagious superficial bacterial infection of the skin that affects mostly children. Most cases are caused by *Staphylococcus aureus*, *Streptococcus pyogenes,* or a mixture of both organisms. Methicillin-resistant *S. aureus* (MRSA) is being observed with increasing frequency in this population. Impetigo is currently being treated with antibiotic ointments, to which bacteria may develop resistance. NVC-422 (*N,N*-dichloro-2,2-dimethyltaurine) is a non-antibiotic antimicrobial agent with potent activity against viruses, yeasts, fungi, and bacteria [(1)]. NVC-422 was delivered in a polymeric gel that was used to evaluate safety and clinical efficacy in treating impetigo in pediatric patients in a pilot study.

Methods. Children aged 2 - 12 years with primary nonbullous impetigo were randomized after written informed consent by their parent or guardian. This dose-ranging parallel group study tested 3 different treatments in an effort to determine the therapeutic dose for further study: a low, medium, and high dose. Sixty subjects were randomized in each dose group in 2 phases of the study. Treatment was administered 3x daily for 7 days to all randomized subjects. Response was measured by the Skin Infection Rating Scale (SIRS) and microbiological eradication.

Results. A total of 129 patients were randomized. Clinical and microbiological success was seen in 84% - 92% of all evaluable subjects after completion of treatment, and at follow-up one week later. The majority of the infections were *S. aureus*, with approximately 10% of those being MRSA, which responded at the same rate as non-MRSA infections. About 13% of the infections were mixed infections or *S. pyogenes* alone. Approximately 5% of subjects had a treatment emergent transient adverse event with a possible causal relationship to treatment.

Conclusion. Based on the results of this study, NVC-422 is a potentially useful novel, non-antibiotic, anti-microbial drug for the treatment of impetigo and further studies are warranted.

♦ Methodology

Study Design – Impetigo

- Randomized, sequential group, double-blind study to evaluate the efficacy and safety of three different strengths of NVC-422 Topical Gel (0.1%, 0.5%, 1.5%)
- Treatment: Topical application 3 times per day for 7 consecutive days
- Sequential Design - Part 1: 0.1% & 0.5% NVC-422 (20:40 subjects), Part 2: 0.1% & 1.5% NVC-422 (20:40)
- A total of 120 subjects were to be enrolled and randomized; 40 in each treatment group.
- Four scheduled study visits: **Day 1** - Screening/Treatment Begins, **Day 4** (± 1) - Interim Visit/Safety, **Day 8** (+1) End of Treatment (EOT) and **Day 15** (± 2) Follow-up - Clinical and bacteriological assessments and efficacy evaluations

Skin Infection Rating Scale (SIRS)

- 5 Signs and Symptoms assessed: exudate/pus, crusting, erythema/inflammation, itching, and pain
- Scale (0-3): 0 = absent, 1 = mild, 2 = moderate, 3 = severe

Enrollment Criteria

- 2-12 years of age with a clinical diagnosis of non-bullous impetigo
- ≤10 impetigo lesions in total
- Total SIRS score ≥ 4; at least 3 of 5 signs and symptoms present at baseline and a score of ≥ 1 for exudate/pus
- Gram stain of target lesion showing Gram-positive cocci

Response Criteria

Clinical Response

- Clinical Success - Sufficient resolution of signs and symptoms of infection of the target lesion such that no additional antimicrobial therapy is required to treat the impetigo, as evidenced by the SIRS score of 0 each for exudate/pus, crusting and pain and 0 or 1 each for erythema/inflammation and itching
- Clinical Improvement - SIRS score of 0 for exudate/pus but does not meet all the criteria for clinical success Clinical Failure - SIRS score of 1 or greater for exudate/pus
- Unevaluable - Valid clinical assessment could not be made

Bacteriological Response

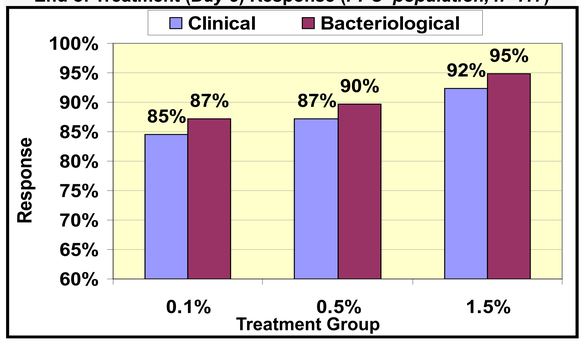
- Bacteriological Success - The causative pathogen isolated from the target lesion at Baseline (*Staphylococcus aureus* and/or *Streptococcus pyogenes*) is eliminated on culture, or clinical response is such that no exudate material was available for culture, as evidence of pathogen eradication
- Bacteriological Failure - Non-eradication from target lesion of the organism that was isolated at Baseline
- Unevaluable - Bacteriological evaluation could not be made due to a reason other than no culture material available

♦ Results

Study Populations		
ITT	*Intent-to-Treat* is all subjects who received at least 1 treatment. Safety analysis was performed on this group	n=129
mITT	*Modified-ITT* is the ITT population who had a positive baseline culture and at least 1 post-baseline visit	n=125
PPC	*Per-Protocol* is the mITT population who completed the study per protocol for clinical and bacteriological evaluations	n=117

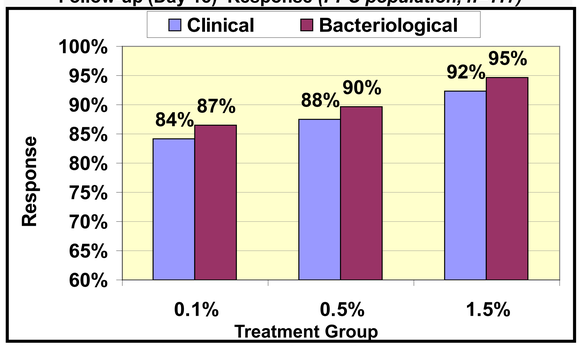
Clinical and Bacteriological Response Results at End of Treatment and Follow-up

End of Treatment (*Day 8*) Response (*PPC population, n=117*)



NOTE: Clinical Response = Success + improvement Bacteriological Response = Success (eradication)

Follow-up (Day 15) Response (*PPC population, n=117*)



(Clinical Response = All subjects were assessed as Success at Follow-up)

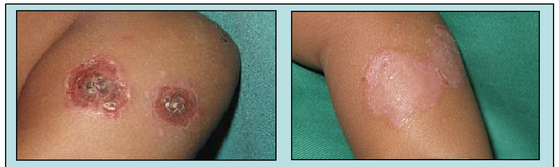
♦ Results

Clinical Response by Infecting Organism at End of Treatment (Day 8)

Treatment Dose	Infecting Organism(s) Isolated at Baseline from Target Lesion				
	S. aureus (MSSA) (n=89)	*S. aureus (MRSA) (n=9)*	*S. pyogenes (n=7)*	*S. aureus (MSSA) and S. pyogenes (n=11)*	*S. aureus (MRSA) and S. pyogenes (n=1)*
NVC-422, 0.1%	22/27 (81%)	4/4 (100%)	4/4 (100%)	3/4 (75%)	*NA*
NVC-422, 0.5%	29/34 (85%)	2/2 (100%)	3/3 (100%)	*NA*	*NA*
NVC-422, 1.5%	26/28 (93%)	3/3 (100%)	*NA*	6/7 (86%)	1/1 (100%)

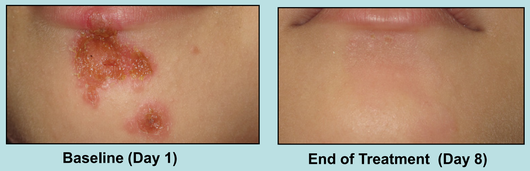
(NA – Organisms were not present in these groups at baseline)

Examples of Successfully Treated Impetigo Lesions



Baseline (Day 1) End of Treatment (Day 8)

S. aureus (MRSA) impetigo infection on forearm of 2 yr old female before and after treatment with NVC-422



Baseline (Day 1) End of Treatment (Day 8)

S. aureus (MSSA) impetigo infection on lip and chin of 3 yr old female before and after treatment with NVC-422

Baseline (Day 1) End of Treatment (Day 8)

S. aureus (MRSA) and *S. pyogenes* mixed impetigo infection on thigh of 2 yr old female before and after treatment with NVC-422

♦ Results

Treatment Emergent Adverse Events ITT Population (n=129)

Adverse events as determined by the investigator during treatment

Adverse Event	**0.1%** (n=43)	**0.5%** (n=45)	**1.5%** (n=41)
Allergy/rash	1	0	0
Contact dermatitis	1	0	0
Dermatitis	0	0	1
Dry skin	0	0	1
Fever	0	1	0
Itching	0	0	2
Total	2	1	4

♦ Discussion and Conclusion

- Overall clinical response rate (success and improvement) in the PPC population was equal to or above 85% in each of the dose groups at EOT (85%, 87%, and 92% in the 0.1%, 0.5% and 1.5% dose groups respectively). This response rate is substantially higher than the response rate anticipated for placebo (30-50%) [(2)]. Similar responses were seen in the mITT population (83%, 84%, and 93% in the 0.1%, 0.5% and 1.5% dose groups respectively).
- Response rates for MRSA infections were 100% (10/10) across all treatment groups in the PPC population, whether MRSA was the sole organism or in a mixed infection.
- All subjects that were Clinical Responders at Day 8 that returned for the follow-up visit at Day 15 were clinical successes with a SIRS score of 0 (*n=103*). There were no recurrences of infection at the follow-up visit (Day 15) in any treatment groups.
- Bacteriological response rates of equal to or above 84% were very similar to clinical response rates at both EOT and follow-up.
- The clinical and bacteriological response rates across the treatment groups suggest a dose response, although differences were not statistically significant.
- Adverse events (7/129, 5.4%) were mild to moderate in severity and predominantly were local reactions at the application site. All adverse events resolved after the end of treatment.
- The rate for subject treatment completion was 96%, and 82% of the subjects returned for the Day 15 (follow-up) visit.
- This proof-of-concept study demonstrates the activity of NVC-422 topical gel in the treatment of impetigo.

♦ References

1. Wang L, Khosrovi B, Najafi R, *"N-Chloro-2,2-dimethyltaurines: a new class of remarkably stable N-chlorotaurines" Tetrahedron Letters 49 (2008) 2193–2195*
2. FDA Briefing Document for Anti-Infective Drugs Advisory Committee Meeting, November 18, 2008 - Justification for the Non-Inferiority Margin for the Treatment of complicated Skin and Skin Structure Infections