

LTX-109

- X A synthetic protein fragment - a peptidomimetic
- K High stability against degradation
- > Prooduced synthetically in large scale
- Content Cost of Synthesis



Chemical structure of LTX-109

Background

LTX-109 is a novel antimicrobial drug in clinical development for skin infections and nasal decolonization of MRSA. The drug mimics the effects of natural antimicrobial peptides in a synthetic small molecule. LTX-109 has demonstrated a broad activity against several Gram (+) and Gram (-) bacteria in vitro, as well activity against a range of yeast and fungal species. The compound is equally effective against antibiotic-resistant species such as methicillin resistant Staphylococcus aureus (MRSA), vancomycin-resistant *Enterococci* (VRE) and multi-resistant *Pseudomonas* isolates. The ultra-rapid membrane lysing mode of action may result in a lower propensity to resistant development and a rapid bactericidal mechanism of action, as shown in *in vitro* studies. To date LTX-109 demonstrates no *in vitro* cross-resistance with other classes of antibiotics.

The current data describe the GLP toxicology / safety program supporting first entry into man.

Methods

A comprehensive panel of GLP toxicology and safety tests was performed according to current ICH regulatory guidelines at the Charles River Laboratories testing facility in Edinburgh, UK. These were designed to satisfy US and EU regulatory bodies, allowing entry into early-stage clinical testing (i.e. phase I and phase II) of a topical formulation.

Evaluation of the Preclinical Safety and Tolerability Profile of LTX-109 - A Novel Antimicrobial Drug

B. MORTENSEN, A. FUGELLI AND W.M. OLSEN Lytix Biopharma, Norway

Results

All GLP studies revealed a good safety and tolerability profile of LTX-109, supporting entry into man. Topical repeat dosing three times daily with up t 14 days is supported by safety margins of 4.8 and 2.56 times in rat and mini-pig respectively.

Repeat dose topical administration three times daily for up to 14 days at concentrations of up to 5% LTX-109 to rats (2.5 mg LTX-109/cm², 120 mg/kg/ mini-pigs (2.5 mg LTX-109/cm², 64 mg/kg/day) with abraded or occluded skin was associated with only minor dose-dependent reversible dermal react no signs of systemic toxicity.

No findings warranted further investigation.

Species	Topical Treatment (conc. x mL x cm ² / day x 3 times daily)	Dose (mg/kg/day)	Animal/ Human Max. Daily Dose Ratio (mg/kg/day)
Rat ^a	5% x 0.2 x 4 x 3	120	4.8
Mini-pig ^b	5% x 6.4 x 128 x 3	64	2.56
Human ^c	5% x 10 x 200 x 3	25	-

^a Based on average body weight of 0.25 kg and body surface area of 0.025m²

^b Based on average body weight of 15 kg and body surface area of 0.74m²

^c Based on average body weight of 60 kg and body surface area of 1.62m², intended maximum daily exposure

Species				
Genotoxicity	Ames Mouse lymphoma chromosome abe Rat micronucleus			
Acute toxicology – i.v. route	Rat - MTD / PK Dog - MTD / PK			
Repeat dosing – dermal route	14d rat - TID topical dosing 14d mini-pig - TID topical dosing			
Safety Pharmacology	hERG Rat Irwin screen Dog telemetered CVR study			
Tolerance/sensitization	Mouse local lymph node assay			
Phototoxicity	UV screen			
ADME	CYP P450 Induction, inhibition Hepatocyte, skin and plasma metal Plasma protein binding			

Lytix Biopharma

g/day)	and
ctions	and

orration	
erration	

abolism

Conclusions

- All GLP studies revealed a good safety and tolerability profile of LTX-109 allowing entry into man
- The comprehensive program was designed to satisfy US and EU regulatory authorities
- LTX-109 has been tested in Phase I and two Phase I/IIa trials with good tolerance, minimal systemic bioavailability
- LTX-109 has demonstrated Proof-of-Concept in decolonisation of nasal MRSA / MSSA.
- Further Phase II studies are planned to demonstrate efficacy in larger patient populations.

LTX-109

- Key Novel mechanism of action
- Stread spectrum of activity
- Low propensity for resistance development and active against drug-resistant strains
- C Effective against fungal and bacterial biofilms
- Superior efficacy compared to market leaders (Bactroban[®], Fucidin[®], Altabax[®]/Altargo[®])