Topical Interferon Alpha-2b – A novel therapy under clinical development for the treatment of HPV induced cervical intraepithelial neoplasia grade 1 or 2 lesions of the uterine cervix

Heman Chao, Praveen Kumar, Terri Hinkle, John Docherty, Donald Segal
Helix BioPharma Corp. Aurora Ontario Canada

Abstract

Currently there are no pharmaceutical treatments for millions of women diagnosed with potentially precancerous. HPV-induced CIN 1 or 2 lesions each year, and available invasive/surgical techniques are potentially associated with complications and side effects. For these patients, clinical management usually consists of watchful waiting with frequent Pap smears, HPV testing, colposcopy and/or colposcopic biopsies, with invasive/surgical techniques utilized only in the case of long-term persistence and/or progression of the lesions. As a result, patients may have to endure months or even years of observation and associated psychological stress before medical intervention is introduced. Interferon alpha-2b is a potent immunomodulatory compound that has been previously shown to be effective against a variety of benign and neoplastic skin lesions when administered by injection. Topical Interferon Alpha-2b (TIFNα2b) is a cream dosage form of recombinant interferon alpha-2b designed for easy use intrasynthetically where injectable drug administration is cumbersome. Topical Interferon Alpha-2b uses Helix BioPharma Corp’s proprietary Biphaxis™ lipid vesicles to encapsulate, stabilize and formulate interferon alpha-2b for topical administration, using a vaginal applicator for convenient self-application by patients. Topical Interferon Alpha-2b has been assessed in two open label Phase II studies in patients with low-grade cervical lesions, and shown to be effective and well tolerated. Using colposcopically directed biopsy to determine the treatment’s effectiveness, 71.4% of the women in the most recently completed study no longer had CIN 1 or 2 lesions following treatment. Helix is currently in the process of pursuing regulatory authorizations for the final pivotal efficacy trial stage of development for this novel product candidate.

Introduction

Delivery of macromolecules into the body, other than via parenteral administration, poses a significant challenge. Systemic delivery exposes healthy tissues to the drug and can result in toxic side effects. In addition, systemic delivery is partial which can result in poor patient compliance. Topical formulations provide better patient compliance versus injections or intravenous infusions as they are needle-free and can be self administered by the patient. Development of a flexible, easy to manufacture, dermal or transdermal drug delivery system for macromolecules would help optimize a drug’s efficacy, safety and compliance while minimizing side effects.

The outer most layer of skin, the stratum corneum (Figure 1) is formed of 15-20 layers of corneocytes, acts as a barrier to prevent external molecules and microbes from entering the body and systemic circulation. In addition, the larger and more hydrophobic the molecule the more difficult it is to deliver the drug through the skin (1,6). There are currently no effective pharmaceutical topical delivery systems for biotechnology derived macromolecule drugs.

Introduction Cont’d

Biphaxis™ Topical Drug Delivery System

Biphaxis™ is a liposome-based technology designed to enable both lipophilic and hydrophilic molecules, to be delivered into (glass) DNA (4) and interferon(5) or through (insulin (2),3) the skin. The Biphaxis™ cream contains phospholipid vesicles which are multimolecular structures with between 15 and 20 layers separated in an oil-in-water micromulsion (Figure 2). The layers are made primarily from phospholipids, which trap the micromulsion containing interferon alpha-2b in the intercellular spaces. No organic solvents are used in manufacture, so there is no risk of residual solvents in the final Biphaxis™ preparations.

Topical Interferon Alpha-2b (TIFNα2b, 2MUg, 5g), a white smooth cream, was manufactured by combining vesicle forming lipids with micromulsion using routinely employed pharmaceutical industry manufacturing equipment at the 1.0 kg or 8.5 kg level for studies, and was packaged in polypolyethylene tubes. The formulation was tested for potency, pharmacoprophylactic and microbiological attributes, and found to be stable under refrigerated conditions. The formulation was tested in a preclinical setting before proceeding to clinical studies. The mechanism by which Biphaxis™ delivers compounds into skin has not been fully elucidated. It is believed that Biphaxis™ cream constituents interact with the corneocytes present in the stratum corneum resulting in a transient change in the permeability and fluidity of the skin to facilitate paracellular drug delivery, whereby the vesicles degrade and the drug molecules access the underlying skin layers (Figure 3).

Two Open Label Phase II Clinical Studies Completed

Completed Clinical Study #N002 / HPV001:
- Safety / efficacy study
- 41 patients (treatment vs. placebo control)
- 18 doses TIFNα2b + 6 week follow-up

Completed Clinical Study #N005:
- Pharmacokinetic / safety / efficacy study
- 14 patients (no control)
- 35 doses TIFNα2b + 2 week follow-up

Figure 1. Cross sectional diagram of the structure of human skin

We have developed a unique topical drug delivery system called Biphaxis™ that enables dermal or transdermal delivery of a variety of small and large molecules (2,3). Drugs formulated with the Biphaxis™ technology can be developed and manufactured using routinely used industrial pharmaceutical equipment and pharmacoceutical excipients.

Figure 2. Illustration of a Biphaxis™ vesicle

Figure 3. Proposed mechanism of drug delivery through the skin. When drug-containing Biphaxis™ vesicles are applied to the skin, temporarily enhanced fluidity of the epidermal intercellular layers is induced. This enables the vesicles to enter the skin, and then to degrade releasing the active compound

Clinical Study #N005

TIFNα2b was well tolerated

No significant systemic penetration

Peripheral CIN resolution

Clinical Study #N002/HPV001

Pap Smear Resolution (Pap15-IDC)

CIN Resolution

28.6% CIN 1 or 2

No CIN

71.4%

U.S. Phase III /III Trial Approval Pending

Study INFO3 Planned Trial Design:
- 402 patients (treatment vs. placebo control)
- 35 doses of TIFNα2b + follow-up 1-year
- Primary endpoint CIN 1/2 and Pap smears resolution at 1 year

Clinical held by the FDA (Nov 19, 2010) pending submission additional product analytical information satisfactory to FDA

European Phase III Trial Under Development

European CTA under development for planned parallel confirmatory Phase III pivotal efficacy trial

References


Contact Information

Helix BioPharma Corp
3-205 Industrial Parkway South
Aurora Ontario Canada L4G 6X7
Tel: +1 (905) 841-2300
Fax: +1 (905) 841-2244
Email: helix@helixbiopharma.com
www.helixbiopharma.com

Forward-looking Statements

Statements regarding planned clinical trials are forward-looking statements and assume that all pre-conditions will be met. The trials may not occur as a result of certain risks, including without limitation, lack of regulatory approval, financing or strategic partner support.