Interferon-α Amarillo Biosciences
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Amarillo Biosciences is developing low-dose oral interferon-α (IFNα; Veldona) as a potential treatment for primary Sjögren’s syndrome, oral mucositis in cancer patients, hepatitis B and C virus (HBV and HCV) infections, and bone marrow disorders [229625]. The company is also developing a topical formulation of IFNα for the potential treatment of genital warts. The product is registered in Ghana for the treatment of HIV infection [284558], [331017]. In October 2001, Amarillo licensed rights to its low-dose oral IFNα to Atrix Laboratories for the Orphan indications of oral papillomavirus and Behçet’s disease [424032].

Introduction
Interferon-α (IFNα) has been used to treat many types of cancers and viral infections, normally using quite high doses and frequent dosing regimens. The route of administration has most often been parenteral and has resulted in numerous side effects including, skin disorders, flu-like symptoms, bone marrow suppression, gastrointestinal disorders, cardiac dysfunction and CNS abnormalities that can trigger depression and suicidal thoughts [398730]. To reduce such effects, Amarillo Biosciences has developed a low dose natural human oral IFNα (Veldona). Among the indications for usage are AIDS-related complex [229629], Behçet’s disease [354036], bone marrow diseases [243579], fibromyalgia [415930], oral mucositis [229629], Sjögren’s syndrome [395224], xerostomia associated with Sjögren’s syndrome [395396] and cytomegalovirus (CMV) [267059], hepatitis B virus (HBV) [398547], hepatitis C virus (HCV) [229629] and papillomavirus [398547] infections.

Synthesis and SAR
IFNα is formulated in anhydrous crystalline maltose; a 200 mg lozenge may contain from 15 to 1600 IU of natural human IFNα [398730]. The IFNα in this formulation is stable for longer than 18 months at room temperature and for five years at 4°C.

Pharmacology
In an interesting study of the effects of low-dose IFNα on CMV infections in mice using immunohistochemistry, antibodies to IFNα localized to the IFN receptor-bearing cells of the gastrointestinal tract and the perivascular smooth muscle cells and lamina propria of the anterior tongue, small intestine and rectum. Thus, these tissues may be the sites where orally administered IFN perturbs the mucosal immune system [448756].

In clinical trials in humans, after the administration of IFNα orally as lozenges, IgM and IgG levels transiently decreased. However, as cytokine IL-5 levels rose, apparently in response to the IFN treatment, both immunoglobulin levels returned to baseline [448758]. Thus, oral IFNα may modulate the mucosal immune response by stimulating the production of IL-5, which in turn is responsible for the switch from an IgM to an IgA response, a hallmark of mucosal immunity.

Among its other immunomodulatory properties, low-dose IFNα administered via the oral mucosal route may depress certain cytokines such as IL-2 and IL-6, which are associated with the inflammatory destruction of salivary glandular tissue in Sjögren’s syndrome patients [448770].

In addition to its immunomodulatory properties, oral IFNα may also increase the secretion of aquaporins to enhance water transport in the salivary glands, a phenomenon that would help alleviate the dry mouth syndrome associated with Sjögren’s disease [398730], [448770].

In a mouse model of CMV infection, an oral dose of 10 IU of IFNα inhibited murine CMV replication in all organs tested, while a dose of 20,000 IU given intraperitoneally achieved the same result [398547]. Studies also showed that CMV infections in several strains of mice could be controlled during the early or acute phase of infection. The same low dose of IFNα also controlled virally-induced myocarditis [285082].

Metabolism
No data are currently available.

Toxicity
In antiviral model studies, low dose oral IFNα (10 IU) was as efficacious as high dose parenteral IFNα (20,000 IU) in treating viral diseases [398547]. No toxicity has been reported to date.
Clinical Development

Phase I
- Oral mucositis
  Oral IFNα was used to treat oral mucositis in a phase I/II trial at three oncology research centers. A clinically significant reduction in oral mucositis was achieved in six of 11 patients receiving a combination of IFNα and chemotherapy, compared to a previous cycle of chemotherapy without IFNα [229629].

HCV infection
  Patients with chronic HCV-infections treated with low-dose oral IFNα followed by a standard course of parenteral IFNα had an initial response rate twice that of patients given parenteral IFNα alone [229629].

HBV infection
  Safety and efficacy studies of IFNα therapy in patients with chronic HBV-infections performed at two clinical centers in Poland demonstrated that oral IFNα therapy resulted in fewer side effects than injectable IFN [229629]. Data from these trials involving patients with chronic active HBV infection also indicated that the numbers of responders to IFNα therapy in the group receiving low-dose oral IFNα did not significantly differ from the group receiving parenteral IFNα [398547].

AIDS-related symptoms
  In a trial involving the treatment of 14 HIV-infected men with human papillomavirus (HPV)-positive oral warts with oral IFNα, eight patients completed 40 weeks of treatment. The warts partially decreased in four patients, slightly in one patient and completely in one patient. Two patients did not respond to treatment. The mean wart area in responsive patients was reduced more than 4-fold, and the numbers of warts were more than halved [398547].

A clinical trial of low-dose oral IFNα therapy for the treatment of AIDS-related symptoms was initiated in 1996 [449493], [449498]. Three different forms of oral IFNα: Veldona, Alferon LDO (Interferon Sciences Inc) and Fermunere, were tested for efficacy and safety. The trial closed prematurely, however, because of a lack of efficacy and little or no positive effects against opportunistic infections [386969], [449497].

Bone marrow disorders
  In 1997, trials began in 50 patients with rare bone marrow proliferation disorders. Ten patients, each with either angioenic myeloid metaplasia, polycythemia vera or primary thrombocytosis were given low oral doses daily for 6 to 12 months to relieve signs and symptoms associated with these disorders [243579]. No data from this study are currently available.

Phase II
- Fibromyalgia syndrome
  A 3-month, multicenter, phase II trial involving 89 patients evaluated the benefit of low-dose IFNα in the relief of morning joint stiffness, a significant problem amongst fibromyalgia sufferers. In the double-blinded, placebo-controlled trial, the patients were divided into three groups and each individual was given three lozenges a day, with different doses for each group. The first group received three lozenges containing 50 IU of Veldona, the second group received one 50 IU lozenge and two placebo lozenges, and the final group received three placebo lozenges. All three groups reported a reduction in morning joint stiffness and there was no significant difference between the treated and untreated groups. There was also no significant difference between the once- and three-times daily groups [395042]. However, upon re-analysis of data and exclusion of patients who could attribute their fibromyalgia to an injury, 82 patients given a single dose of Veldona experienced significant improvement compared to placebo in five variables of stiffness, and non-significant improvement in eight other symptom variables including three relating to pain [415930].

Sjögren's syndrome
  Sjögren's syndrome is characterized by dry eyes and dry mouth because of disease in the lachrymal and salivary glands. Patients experience significant discomfort and are susceptible to optical damage and oral disease. A phase II, double-blind, placebo-controlled trial was initiated to determine the safety and efficacy of Veldona for treating Sjögren's syndrome [270896], [448760], [448761]. This trial used four different dosage regimens administered over the 12 week treatment period; low doses of 150 or 450 IU were administered once- or three times daily as a lozenge [448761]. The multicenter study population was divided into groups of high and low baseline tear and saliva production for analysis, and a dose of Veldona significantly increased salivary flow, improved mouth comfort and decreased the sensation of eye dryness in the high baseline population, probably indicating a better treatment effect in the less severely affected patients. Adverse events were comparable to placebo [270896].

Phase III
- Sjögren's syndrome
  A phase III, 24-week, double-blind, placebo-controlled trial enrolled 241 patients with primary Sjögren's syndrome to test the efficacy of Veldona. Patients were treated three-times daily with a lozenge containing either 150 IU of IFNα or a placebo. Among the evaluable patients there was a significant increase in unstimulated whole saliva (UWS) production in those who had received Veldona compared to those who received placebo, which correlated strongly with subjective improvements in oral, throat and nasal dryness as determined by visual analog scales [361996].

In a second phase III study involving an additional 250 patients, a similar improvement in saliva production was seen, with highly significant improvements in both UWS and stimulated whole saliva production of more than double that of the placebo group, 24 weeks after initiation of treatment [395224].

Open or proposed new trials
- Behcet's disease
  Behcet's disease is a severe chronic relapsing inflammatory disorder marked by oral and genital ulcers, eye inflammation (uveitis), skin lesions, as well as varying multisystem involvement including the joints, blood vessels, central nervous system and gastrointestinal tract. The oral
lesions are an invariable sign occurring in all patients at some time during the disease. A clinical development program began in 2000 [354036] based on preliminary data suggesting efficacy of Veldona in treating Behçet’s disease [448762].

**HBV infection**

In June 1999, the company signed an agreement with the North China Pharmaceutical Corp of Shijiazhuang, for the development, manufacturing and marketing of Amarillo’s low-dose IFNα for HBV infection in China. A major clinical study began in August 1999 but no data from the study are currently available [328162].

**Idiopathic pulmonary fibrosis**

In November 2001, Amarillo was awarded an Advanced Technology Program grant to test its oral IFNα as a treatment for idiopathic pulmonary fibrosis (IPF), an interstitial lung disease of unknown cause. This US$100,000 grant is intended to support a pilot study involving 20 patients [428590].

**Side Effects and Contraindications**

The incidence of traditional side effects from IFNα therapy, including fever, rash, diarrhea, flu-like symptoms, arthralgia, weight loss and malaise, were significantly reduced among the recipients of oral IFNα compared to those receiving higher dose parenteral IFNα [267059]. In a preliminary clinical trial conducted in a major HIV treatment center in San Francisco, minimal side effects along with some efficacy data were reported for the formulation administered as a lozenge [379875]. In a number of other clinical settings, the low-dose oral administration had a significantly better side effect profile than parenteral administration. For example, only a 1.5% incidence of fever was recorded compared to 92 and 86% for Roferon-A (Hoffmann-La Röche Inc) and Intron-A, respectively [398547]. This relative lack of toxicity has since been verified in a number of other clinical trials for a variety of disease conditions.

**Current Opinion**

Veldona promises to be a very useful drug in ameliorating the effects of many different diseases. However, little data has been forthcoming from the many clinical trials supported by Amarillo. Of the trials reported, the data support the usefulness of Veldona in treating Sjögren’s syndrome and perhaps fibromyalgia. Until more efficacy data are presented for the other diseases currently being considered, it will be difficult to assess the impact that this drug may have, although it could be considerable, especially as it has a good side effect profile and compliance is favorable.

Amarillo has numerous trials planned to test the efficacy of Veldona against a variety of clinical diseases. From a corporate perspective, one questions whether they have the capital to support all these projects, and from the scientific viewpoint, whether they can adequately monitor and analyze the data from so many different trials involving so many different clinical applications.

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**Licensing**

**Atrix Laboratories Inc**

In October 2001, Amarillo licensed rights to its low-dose oral IFNα to Atrix Laboratories for the Orphan indications of oral papillomavirus infection and Behçet’s disease. Under the terms of the deal, Atrix paid US$485,000 for licensing. Orphan Drug designations and clinical supplies. Atrix is to fund R&D of the product. As part of the agreement, Amarillo will receive payments for specific clinical and regulatory milestones and will receive a royalty based on sale of any product developed [424032].

**Interferon Sciences Inc**

Amarillo has entered into a licensing agreement granting Interferon Sciences use of the company’s patented technology for the use and sale of IFNα products worldwide, except for Japan, in exchange for a royalty on net sales of licensed products [229625].

**Key Oncologics (Pty) Ltd**

In May 2000, Key Oncologics entered an agreement with Amarillo for the development and marketing on Amarillo’s low-dose, orally administered IFNα for the potential treatment of HIV, infection, in South Africa, Zimbabwe, Botswana and Namibia. As part of the agreement, Amarillo will supply IFNα to Key. Key has responsibility for obtaining all government approvals in South Africa for both clinical trials and marketing [366524].

**Mitsubishi Corp**

In November 1990, the company entered into marketing agreement appointing Mitsubishi as its exclusive marketing representative worldwide for low-dose IFNα products, except for the US, Japan, Thailand and certain countries in Africa [229625].

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**Development history**

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<tr>
<th>Developer</th>
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<th>Status</th>
<th>Indication</th>
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<td>Ghana</td>
<td>Registered</td>
<td>Hepatitis B virus infection</td>
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<td>Amarillo Biosciences Inc</td>
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<td>Atrix Laboratories Inc</td>
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Development history (continued)

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Literature classifications

**Chemistry**

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<th>Study Type</th>
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<tr>
<td>Synthesis</td>
<td>IFNα is formulated in anhydrous crystalline maltose.</td>
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**Biology**

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<th>Experimental Model</th>
<th>Result</th>
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<td><em>in vivo</em></td>
<td>Safety and efficacy.</td>
<td>Mouse model of CMV infection.</td>
<td>CMV infections could be controlled during the early or acute phase of infection. An oral dose of 10 IU of IFNα was as effective as an injected dose of 20,000 IU.</td>
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**Metabolism**

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<thead>
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<th>Result</th>
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<td><em>in vivo</em></td>
<td>Safety and efficacy.</td>
<td>Mouse model of CMV infection.</td>
<td>IFNα localizes in IFN receptor-bearing cells of the lamina propria of the GI tract and perivascular smooth muscle cells.</td>
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**Clinical**

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<td>Efficacy</td>
<td>A phase II trial in 89 patients with fibromyalgia.</td>
<td>A significant improvement, scored across five variables of stiffness, was seen among recipients of IFNα compared to those receiving placebo.</td>
<td>415990</td>
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<td>IFNα significantly increased stimulated saliva flow, improved mouth comfort and decreased the sensation of dryness in the high baseline population.</td>
<td>270896</td>
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<td>Efficacy</td>
<td>A phase III, 24-week, double-blind, placebo-controlled trial in 241 patients with Sjögren's syndrome.</td>
<td>IFNα treatment caused a significant increase in unstimulated whole saliva production, which correlated strongly with subjective improvements in oral dryness, throat dryness and nasal dryness, as determined by visual analog scales.</td>
<td>361996</td>
</tr>
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<td>IFNα treatment caused significant improvements in UWS and stimulated whole saliva production of more than double that seen in the placebo-receiving group.</td>
<td>395224</td>
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Associated patent

**Title**: Treatment of immuno-resistant disease with low-dose interferon.

**Assignee**: Texas University System

**Publication**: US-0519382 28-MAY-91

**Priority**: US-00927834 06-NOV-86

**Inventors**: Cummins jR, Joseph M.

**Associated references**

228888 Amarillo BioSciences begins phase II of clinical trials in treatment of Sjögren's syndrome. Amarillo Biosciences Inc PRESS RELEASE 1996 December 03

229625 Amarillo Biosciences Inc. Amarillo Biosciences Inc COMPANY BROCHURE 1996 December

229629 2,000,000 shares Amarillo Biosciences Inc common stock. Amarillo Biosciences Inc COMPANY PROSPECTUS 1996 August 07

- This prospectus reports the use of IFNα for treatment of oral mucositis, AIDS-related complex, hepatitis C virus infection and other diseases.

230259 Clinical trials update. SCRIP 1996 2189 25

24579 Amarillo Biosciences announces a new clinical trial in patients with bone marrow disorders. Amarillo Biosciences Inc PRESS RELEASE 1997 April 24

245873 Amarillo Biosciences announces a new clinical trial in hepatitis C patients. Amarillo Biosciences Inc PRESS RELEASE 1997 May 13

254793 Amarillo Biosciences moves towards phase III trial: contracts with PPD Pharmaco for phase III trial management. Amarillo Biosciences Inc PRESS RELEASE 1997 July 14

256262 Amarillo Biosciences reaches target enrolment/phase II Sjögren's syndrome study advancement on track. Amarillo Biosciences Inc PRESS RELEASE 1997 August 06
262077 Amarillo Biosciences' Board of Directors approves additional clinical study funding. Amarillo Biosciences Inc PRESS RELEASE 1997 September 09

264477 Amarillo Biosciences announces new license agreements. Amarillo Biosciences Inc PRESS RELEASE 1997 September 30

267059 Amarillo Biosciences technology receives additional scientific validation; investigator validates systemic effect of low dose oral interferon. Amarillo Biosciences Inc PRESS RELEASE 1997 October 23

270966 Amarillo Biosciences reports positive phase II Sjogren's syndrome study data. Amarillo Biosciences Inc PRESS RELEASE 1997 December 01

273327 Trials planned. CLIN TRIALS MONITOR 1998 7 1 1-5

• This paper gives details of a planned phase III randomized, double-blind, placebo-controlled trial of low-dose oral IFNα to treat Sjogren's syndrome.

284558 Amarillo Biosciences receives permission to sell low dose oral interferon α for hepatitis B - Ghana's 1.9 million sufferers could benefit from new product. Amarillo Biosciences Inc PRESS RELEASE 1998 April 20


• This paper reports the closing of the first trial treating 300 patients with IFNα, with data justifying the termination of the trial.

395224 Amarillo Biosciences Inc announces completion of phase III Sjogren's syndrome clinical trial. Amarillo Biosciences Inc PRESS RELEASE 2001 January 05


398547 Developing a low dosage therapeutic interferon. Fox GC, SMI CONF - CYTOKINES AS DRUG TARGETS THER 2001 January 29-30 1-31


415930 Amarillo Biosciences Inc announces supplemental analysis of phase II fibromyalgia syndrome clinical trial. Amarillo Biosciences Inc PRESS RELEASE 2001 July 17

424032 Amarillo Biosciences Inc licenses rights to low dose oral interferon for Orphan Drug indications. Amarillo Biosciences Inc PRESS RELEASE 2001 October 02

427478 Atrix Laboratories reports 2001 third quarter financial results. Atrix Laboratories Inc PRESS RELEASE 2001 October 30

428590 Amarillo Biosciences' orally-administered interferon-α to be tested as treatment for idiopathic pulmonary fibrosis under grant awarded to Texas Tech University Health Sciences Center. Amarillo Biosciences Inc PRESS RELEASE 2001 November 07


• A review of current and possible future therapies for treatment of Behçet's disease.


• This paper describes the mechanism of binding and activation of mucosal immunity.

448756 Oral administration of interferon-α induces a transient decline in oral mucosal immunoglobulins and an increase in interleukin-5. Naylor PH, Naylor CW, Hendrix S, Leveque FG J INTERFERON CYTOKINE RES 1999 19 8 953-959


• Official NIAID announcement of the first trial for treating AIDs patients with Veldona.


• Official NIAID announcement of the closing of first trial for treating AIDs patients with Veldona.


• A more detailed description of the announcement of the first trial treating AIDs patients with Veldona.