GENESOFT PHARMACEUTICALS INC
Form 425
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Filed by Genome Therapeutics Corp.

Pursuant to Rule 425 under the Securities Act of 1933

and deemed filed pursuant to Rule 14a-12

of the Securities Exchange Act of 1934

Subject Company: GeneSoft Pharmaceuticals, Inc.

Commission File No. 0-10824

This filing relates to the proposed merger transaction pursuant to the terms of that certain Agreement and Plan of Merger and Reorganization, dated as of November 17, 2003 (the Merger Agreement), by and among Genome Therapeutics Corp. (Genome Therapeutics), Guardian Acquisition, Inc., a wholly owned subsidiary of Genome Therapeutics, GeneSoft Pharmaceuticals, Inc. (Genesoft) and the Stockholders Representative named therein.

This filing is made for the purpose of filing certain prescribing information regarding FACTIVE®. The materials are also available on Genome Therapeutics website, www.genomecorp.com.

Forward-Looking Statements

This document may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements represent our management s judgment regarding future events. Forward-looking statements typically are identified by use of terms such as may, will, should, plan, expect, intend, anticipate, estimate, and similar words, although some forward-looking statements are expressed differently. We do not plan to update these forward-looking statements. You should be aware that our actual results could differ materially from those contained in the forward-looking statements due to a number of risks affecting our business. These factors include the risk that the proposed merger may not be approved by stockholders of Genome Therapeutics or Genesoft, Genome Therapeutics or Genesoft s inability to satisfy the closing conditions of the merger, including the condition of raising additional capital to finance the combined company, the risk that the two companies businesses will not be integrated successfully and the significant costs related to the proposed merger . Upon completion of the merger, our business will be significantly dependent upon the combined company s ability to launch the commercial sale of FACTIVE®, and, due to the limitations on our resources and experience in commercializing products, there can be no assurance that we will be able to successfully launch FACTIVE®. We continue to be subject to the risks related to our lead product candidate, Ramoplanin, such as (i) our inability to obtain regulatory approval to commercialize Ramoplanin due to negative, inconclusive or insufficient clinical data and (ii) delays in the progress of our clinical trials for Ramoplanin, and increased cost, due to the pace of enrollment of patients in the trials or fluctuations in the infection rate of enrolled patients. We are also subject to risks related to our inability or the inability of our alliance partners to (i) successfully develop products based on our genomics information, (ii) obtain the necessary regulatory approval for such products, (iii) effectively commercialize any products developed before our competitors are able to commercialize competing products or (iv) obtain and enforce intellectual property rights. In addition, we are subject to the risk factors set forth in Exhibit 99.1

to the Company s Quarterly Report on Form 10-Q for the quarter ended September 27, 2003 and those set forth in other filings that we may make with the Securities and Exchange Commission from time to time.

Additional Information About the Transaction and Where You Can Find It

Genome Therapeutics will file a proxy statement/prospectus and other documents concerning the proposed merger transaction with the SEC. **Investors are urged to read the proxy statement/prospectus when it becomes available and the other relevant documents filed with the SEC because they will contain important information.**

You will be able to obtain the proxy statement/prospectus and other related documents free of charge at the website maintained by the SEC at www.sec.gov. In addition, you may obtain documents filed with the SEC by Genome Therapeutics free of charge by requesting them in writing from Genome Therapeutics Corp., 100 Beaver Street, Waltham, MA 02453 Attention: Investor Relations, telephone: (781) 398-2300.

Genome Therapeutics and Genesoft and their respective directors, executive officers and other members of their management and employees, may be deemed to be participants in the solicitation of proxies from their respective shareholders in connection with the merger. Information about the directors and executive officers of Genome Therapeutics and their ownership of Genome Therapeutics shares is set forth in the proxy statement for Genome Therapeutics 2003 annual meeting of shareholders, filed with the SEC on April 2, 2003. Investors may obtain additional information regarding the interests of such participants by reading the proxy statement/prospectus when it is filed with the SEC.

This document shall not constitute an offer to sell or the solicitation of an offer to buy any securities of Genome Therapeutics.

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Labeling

July 17, 2003 version

PRESCRIBING INFORMATION

FACTIVE® (gemifloxacin mesylate) Tablets

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FACTIVE and other antibacterial drugs, FACTIVE should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FACTIVE (gemifloxacin mesylate) is a synthetic broad-spectrum antibacterial agent for oral administration. Gemifloxacin, a compound related to the fluoroquinolone class of antibiotics, is available as the mesylate salt in the sesquihydrate form. Chemically, gemifloxacin is (*R,S*)-7-[(4*Z*)-3-(aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]- 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid. The mesylate salt is a white to light brown solid with a molecular weight of 485.49. Gemifloxacin is considered freely soluble at neutral pH (350 µg/mL at 37°C, pH 7.0). Its empirical formula is $C_{18}H_{20}FN_5O_4 \bullet CH_4O_3S$ and its chemical structure is:

Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.

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CLINICAL PHARMACOLOGY

Pharmacokinetics

The pharmacokinetics of gemifloxacin are approximately linear over the dose range from 40 mg to 640 mg. There was minimal accumulation of gemifloxacin following multiple oral doses up to 640 mg a day for 7 days (mean accumulation <20%). Following repeat oral administration of 320 mg gemifloxacin once daily, steady-state is achieved by the third day of dosing.

Absorption and Bioavailability

Gemifloxacin, given as an oral tablet, is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations of gemifloxacin were observed between 0.5 and 2 hours following oral tablet administration and the absolute bioavailability of the 320 mg tablet averaged approximately 71% (95% CI 60%-84%). Following repeat oral doses of 320 mg to healthy subjects, the mean ± SD maximal gemifloxacin plasma concentrations (Cmax) and systemic drug exposure (AUC(0-24)) were 1.61 ± 0.51 µg/mL (range 0.70-2.62 µg/mL) and 9.93 ± 3.07 µg•hr/mL (range 4.71-20.1 µg•hr/mL), respectively. In patients with respiratory and urinary tract infections (n=1423), similar estimates of systemic drug exposure were determined using a population pharmacokinetics analysis (geometric mean AUC(0-24), 8.36 µg•hr/mL; range 3.2 47.7 µg•hr/mL.

The pharmacokinetics of gemifloxacin were not significantly altered when a 320 mg dose was administered with a high-fat meal. Therefore FACTIVE tablets may be administered without regard to meals.

Distribution

In vitro binding of gemifloxacin to plasma proteins in healthy subjects is approximately 60 to 70% and is concentration independent. After repeated doses, the in vivo plasma protein binding in healthy elderly and young subjects ranged from 55% to 73% and was unaffected by age. Renal impairment does not significantly affect the protein binding of gemifloxacin. The blood-to-plasma concentration ratio of gemifloxacin was 1.2:1. The geometric mean for Vdss/F is 4.18 L/kg (range, 1.66 12.12 L/kg).

Gemifloxacin is widely distributed throughout the body after oral administration. Concentrations of gemifloxacin in bronchoalveolar lavage fluid exceed those in the plasma. Gemifloxacin penetrates well into lung tissue and fluids. After five daily doses of 320 mg gemifloxacin, concentrations in plasma, bronchoalveolar macrophages, epithelial lining fluid and bronchial mucosa at approximately 2 hours were as in Table 1:

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Table 1. Gemifloxacin Concentrations in Plasma and Tissues (320 mg Oral Dosing)

Tissue	Concentration (mean ± SD)	Ratio compared with plasma (mean±SD)
Plasma	1.40 (0.442) µg/mL	
Bronchoalveolar Macrophages	107 (77) µg /g	90.5(106.3)
Epithelial Lining Fluid	2.69 (1.96) µg /mL	1.99(1.32)
Bronchial Mucosa	9.52 (5.15) µg /g	7.21(4.03)

Metabolism

Gemifloxacin is metabolized to a limited extent by the liver. The unchanged compound is the predominant drug-related component detected in plasma (approximately 65%) up to 4 hours after dosing. All metabolites formed are minor (<10% of the administered oral dose); the principal ones are N-acetyl gemifloxacin, the E-isomer of gemifloxacin and the carbamyl glucuronide of gemifloxacin. Cytochrome P450 enzymes do not play an important role in gemifloxacin metabolism, and the metabolic activity of these enzymes is not significantly inhibited by gemifloxacin.

Excretion

Gemifloxacin and its metabolites are excreted via dual routes of excretion. Following oral administration of gemifloxacin to healthy subjects, a mean (±SD) of 61± 9.5% of the dose was excreted in the feces and 36± 9.3% in the urine as unchanged drug and metabolites. The mean (±SD) renal clearance following repeat doses of 320 mg was approximately 11.6 ± 3.9 L/hr (range 4.6-17.6 L/hr), which indicates active secretion is involved in the renal excretion of gemifloxacin. The mean (±SD) plasma elimination half-life at steady state following 320 mg to healthy subjects was approximately 7 ± 2 hours (range 4-12 hours).

Special Populations

Pediatric: The pharmacokinetics of gemifloxacin in pediatric subjects have not been studied.

Geriatric: In adult subjects, the pharmacokinetics of gemifloxacin are not affected by age.

Gender: There are no significant differences between gemifloxacin pharmacokinetics in males and females when differences in body weight are taken into account. Population pharmacokinetic studies indicated that following administration of 320 mg gemifloxacin, AUC values were approximately 10% higher in healthy female patients compared to males.

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Males and females had mean AUC values of 7.98 µg·h/mL (range, 3.21 42.71 µg·h/mL) and 8.80 µg·h/mL (range, 3.33 47.73 µg·h/mL), respectively. No gemifloxacin dosage adjustment based on gender is necessary.

Hepatic Insufficiency: The pharmacokinetics following a single 320 mg dose of gemifloxacin were studied in patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) liver disease. There was a mean increase in AUC (0-inf) of 34% and a mean increase in Cmax of 25% in these patients with hepatic impairment compared to healthy volunteers.

The pharmacokinetics of a single 320 mg dose of gemifloxacin were also studied in patients with severe hepatic impairment (Child-Pugh Class C). There was a mean increase in AUC (0-inf) of 45% and a mean increase in Cmax of 41% in these subjects with hepatic impairment compared to healthy volunteers.

These average pharmacokinetic increases are not considered to be clinically significant. There was no significant change in plasma elimination half-life in the mild, moderate or severe hepatic impairment patients. No dosage adjustment is recommended in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. (See **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency: Results from population pharmacokinetic and clinical pharmacology studies with repeated 320 mg doses indicate the clearance of gemifloxacin is reduced and the plasma elimination is prolonged, leading to an average increase in AUC values of approximately 70% in patients with renal insufficiency. In the pharmacokinetic studies, gemifloxacin Cmax was not significantly altered in subjects with renal insufficiency. Dose adjustment in patients with creatinine clearance >40 mL/min is not required. Modification of the dosage is recommended for patients with creatinine clearance ≤40 mL/min. (See **DOSAGE AND ADMINISTRATION.)**

Hemodialysis removes approximately 20 to 30% of an oral dose of gemifloxacin from plasma.

Photosensitivity Potential: In a study of the skin response to ultraviolet and visible radiation conducted in 40 healthy volunteers, the minimum erythematous dose (MED) was assessed following administration of either gemifloxacin 160 mg once daily, gemifloxacin 320 mg once daily, ciprofloxacin 500 mg b.i.d., or placebo for 7 days. At 5 of the 6 wavelengths tested (295-430 nm), the photosensitivity potential of gemifloxacin was not statistically different from placebo. At 365 nm (UVA region), gemifloxacin showed a photosensitivity potential similar to that of ciprofloxacin 500 mg b.i.d. and the photosensitivity potential for both drugs were statistically greater than that of placebo. Photosensitivity reactions were

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reported rarely in clinical trials with gemifloxacin (0.039%). (See **ADVERSE REACTIONS**.)

Drug-Drug Interactions

Antacids/Di- and Trivalent Cations: The systemic availability of gemifloxacin is significantly reduced when an aluminum-and magnesium-containing antacid is concomitantly administered (AUC decreased 85%; Cmax decreased 87%). Administration of an aluminum- and magnesium- containing antacid or ferrous sulfate (325 mg) at 3 hours before or at 2 hours after gemifloxacin did not significantly alter the systemic availability of gemifloxacin. Therefore, aluminum- and/or magnesium- containing antacids, ferrous sulfate (iron), multivitamin preparations containing zinc or other metal cations, or Videx® (didanosine) chewable/buffered tablets or the pediatric powder for oral solution should not be taken within 3 hours before or 2 hours after taking FACTIVE tablets.

Calcium carbonate (1000 mg) given either 2 hr before or 2 hr after gemifloxacin administration showed no notable reduction in gemifloxacin systemic availability. Calcium carbonate administered simultaneously with gemifloxacin resulted in a small, not clinically significant, decrease in gemifloxacin exposure [AUC (0-inf) decreased 21% and Cmax decreased].

Sucralfate: When sucralfate (2 g) was administered 3 hours prior to gemifloxacin, the oral bioavailability of gemifloxacin was significantly reduced (53% decrease in AUC; 69% decrease in Cmax). When sucralfate (2 g) was administered 2 hours after gemifloxacin, the oral bioavailability of gemifloxacin was not significantly affected; therefore FACTIVE should be taken at least 2 hours before sucralfate. (See **PRECAUTIONS.**)

In Vitro Metabolism: Results of in vitro inhibition studies indicate that hepatic cytochrome P450 (CYP450) enzymes do not play an important role in gemifloxacin metabolism. Therefore gemifloxacin should not cause significant in vivo pharmacokinetic interactions with other drugs that are metabolized by CYP450 enzymes.

Theophylline: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of theophylline (300 to 400 mg b.i.d. to healthy male subjects).

Digoxin: Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of digoxin (0.25 mg once daily to healthy elderly subjects).

Oral Contraceptives: The effect of an oral estrogen/progesterone contraceptive product (once daily for 21 days) on the pharmacokinetics of gemifloxacin (320 mg once daily for 6 days) in healthy female subjects indicates that concomitant administration caused an average reduction in gemifloxacin AUC and Cmax of 19% and 12%. These changes are not

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considered clinically significant. Gemifloxacin 320 mg at steady-state did not affect the repeat dose pharmacokinetics of an ethinylestradiol/levonorgestrol oral contraceptive product (30 µg/150 µg once daily for 21 days to healthy female subjects).

Cimetidine: Co-administration of a single dose of 320 mg gemifloxacin with cimetidine 400 mg four times daily for 7 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 6%, respectively. These increases are not considered clinically significant.

Omeprazole: Co-administration of a single dose of 320 mg gemifloxacin with omeprazole 40 mg once daily for 4 days resulted in slight average increases in gemifloxacin AUC(0-inf) and Cmax of 10% and 11%, respectively. These increases are not considered clinically significant.

Warfarin: Administration of repeated doses of gemifloxacin (320 mg once daily for 7 days) to healthy subjects on stable warfarin therapy had no significant effect on warfarin-induced anticoagulant activity (i.e., International Normalized Ratios for Prothrombin Time). (See **PRECAUTIONS: Drug Interactions**.)

Probenecid: Administration of a single dose of 320 mg gemifloxacin to healthy subjects who also received repeat doses of probenecid (total dose = 4.5 g) reduced the mean renal clearance of gemifloxacin by approximately 50%, resulting in a mean increase of 45% in gemifloxacin AUC(0-inf) and a prolongation of mean half-life by 1.6 hours. Mean gemifloxacin Cmax increased 8%.

Microbiology

Gemifloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive microorganisms. Gemifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs). Gemifloxacin acts by inhibiting DNA synthesis through the inhibition of both DNA gyrase and topoisomerase IV (TOPO IV), which are essential for bacterial growth. *Streptococcus pneumoniae* showing mutations in both DNA gyrase and TOPO IV (double mutants) are resistant to most fluoroquinolones. Gemifloxacin has the ability to inhibit both enzyme systems at therapeutically relevant drug levels in *S. pneumoniae* (dual targeting), and has MIC values that are still in the susceptible range for some of these double mutants.

The mechanism of action of quinolones, including gemifloxacin, is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to gemifloxacin and other quinolones. There is no known cross-resistance between gemifloxacin and the above mentioned classes of antimicrobials.

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The main mechanism of fluoroquinolone resistance is due to mutations in DNA gyrase and/or TOPO IV. Resistance to gemifloxacin develops slowly via multistep mutations and efflux in a manner similar to other fluoroquinolones. The frequency of spontaneous mutation is low (10^{-7} to $<10^{-10}$). Although cross-resistance has been observed between gemifloxacin and other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gemifloxacin.

Gemifloxacin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP])*.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (penicillin-resistant *Streptococcus pneumoniae)*, and are strains resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae (many strains are only moderately susceptible)

Moraxella catarrhalis

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

The following data are available, **but their clinical significance is unknown.**

Gemifloxacin exhibits in vitro minimal inhibitory concentrations (MICs) of 0.25 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of gemifloxacin in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)

Streptococcus pyogenes

Aerobic gram-negative microorganisms

Acinetobacter lwoffii

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Klebsiella oxytoca

Legionella pneumophila

Proteus vulgaris

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gemifloxacin powder. The MICs should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*:

MIC (µg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5	Intermediate (I)
≥1.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than Susceptible . Strains yielding MIC results suggestive of a nonsusceptible category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b]:

MIC (µg/mL)	Interpretation
≤0.12	Susceptible (S)

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0.25	Intermediate (I)
≥0.5	Resistant(R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Muller-Hinton broth with 2-5% lysed horse blood.

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gemifloxacin powder should provide the following MIC values:

Microorganism		**MIC Range (µg/mL)**
Enterococcus faecalis	ATCC 29212	0.016-0.12
Escherichia coli	ATCC 25922	0.004-0.016
Haemophilus influenzae	ATCC 49247[c]	0.002-0.008
Streptococcus pneumoniae	ATCC 49619[d]	0.008-0.03

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)[1].