INTROGEN THERAPEUTICS INC
Form 10-Q
May 04, 2007

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-Q

(Mark One)

þ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the quarterly period ended March 31, 2007.

or

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to .

Commission file number 000-21291

Introgen Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**74-2704230**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification Number)*

301 Congress Avenue, Suite 1850
Austin, Texas 78701
(Address of principal executive offices, including zip code)
(512) 708-9310
(Registrant s telephone number, including area code)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer or a non-accelerated filer. See definition of accelerated filer and large accelerated filer in Rule 12b-2 of the Exchange Act. (Check one): Large accelerated filer o Accelerated filer þ Non-accelerated filer o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No þ

As of May 3, 2007 the registrant had 43,730,724 shares of its common stock, $0.001 par value per share, issued and outstanding.

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PART I
FINANCIAL INFORMATION

Item 1. Financial Statements

INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES
CONDENSED CONSOLIDATED BALANCE SHEETS
(Amounts in thousands, except per share amounts)

	December 31, 2006	March 31, 2007 (Unaudited)
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 25,578	$ 4,956
Short-term investments	15,767	29,203
Total cash, cash equivalents and short-term investments	41,345	34,159
Marketable securities	6,957	11,004
Prepaid expense and other current assets	397	785
Total current assets	48,699	45,948
Property and equipment, net of accumulated depreciation of $13,976 and $14,255	5,172	4,893
Other assets	290	283
Total assets	$ 54,161	$ 51,124
LIABILITIES AND STOCKHOLDERS EQUITY		
Current Liabilities:		
Accounts payable	$ 2,384	$ 1,538
Accrued liabilities and other	4,817	3,383
Deferred revenue and other	624	624
Current portion of notes payable	917	791
Total current liabilities	8,742	6,336
Notes payable, net of current portion	7,448	7,305
Deferred revenue and other, long-term	923	712
Total liabilities	17,113	14,353
Non-controlling interest in consolidated subsidiary		14
Commitments and Contingencies		
Stockholders Equity:		
Preferred stock, $.001 par value per share; 5,000 shares authorized; 4,900 shares issuable; zero Series A shares issued and outstanding in 2006 and 2007, respectively	44	44

Common stock, $.001 par value per share; 100,000 shares authorized; shares issued and outstanding of 43,591in 2006 and 43,700 in 2007		
Additional paid-in capital	205,350	206,633
Accumulated deficit	(172,260)	(177,877)
Accumulated other comprehensive gain	3,914	7,957
Total stockholders equity	37,048	36,757
Total liabilities and stockholders equity	$ 54,161	$ 51,124

The accompanying notes are an integral part of these condensed consolidated financial statements.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(Amounts in thousands, except per share amounts)
(UNAUDITED)

	Three Months Ended March 31,	
	2006	**2007**
Contract services, grant and other revenue	$ 225	$ 322
Operating costs and expense:		
Research and development, including share-based compensation of $217 in 2006 and $305 in 2007	5,046	3,175
General and administrative, including share-based compensation of $2,021 in 2006 and $950 in 2007	3,796	3,267
Total operating costs and expense	8,842	6,442
Loss from operations	(8,617)	(6,120)
Interest income	299	442
Interest expense	(156)	(179)
Other income	255	254
Loss before non-controlling interest in consolidated subsidiary	(8,219)	(5,603)
Non-controlling interest in consolidated subsidiary		(14)
Net loss	$ (8,219)	$ (5,617)
Net loss per share, basic and diluted	$ (0.22)	$ (0.13)
Shares used in computing basic and diluted net loss per share	37,180	43,655

The accompanying notes are an integral part of these condensed consolidated financial statements.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(Amounts in thousands)
(UNAUDITED)

	Three Months Ended March 31,	
	2006	**2007**
Cash flows from operating activities:		
Net loss	$ (8,219)	$ (5,617)
Adjustments to reconcile net loss to net cash used in operating activities:		
Non-controlling interest in consolidated subsidiary		14
Depreciation	358	279
Share-based compensation	2,238	1,255
Amortization of grant rights acquired	133	
Changes in assets and liabilities:		
(Increase) decrease in other assets	20	(381)
Increase (decrease) in accounts payable	223	(846)
Increase (decrease) in accrued liabilities	(357)	68
Increase (decrease) in deferred revenue and other	(6)	(211)
Net cash used in operating activities	(5,610)	(5,439)
Cash flows from investing activities:		
Purchases of property and equipment	(36)	
Purchases of short-term investments	(15,809)	(13,436)
Net cash used in investing activities	(15,845)	(13,436)
Cash flows from financing activities:		
Payment of offering costs related to sale of common stock		(1,571)
Proceeds from exercise of options for common stock	29	97
Proceeds from notes payable	97	
Principal payments under notes payable	(224)	(269)
Net cash used in financing activities	(98)	(1,743)
Effect of exchange rate changes on cash		(4)
Net decrease in cash	(21,553)	(20,622)
Cash and cash equivalents, beginning of period	28,090	25,578
Cash and cash equivalents, end of period	$ 6,537	$ 4,956
Supplemental disclosure of cash flow information:		
Cash paid for interest	$ 148	$ 171
Cash paid for taxes for the issuance of common stock in connection with the grant of common stock	$ 28	$

Supplemental disclosure of non-cash investing and financing activities:				
Grant rights acquired in asset acquisition	$	30	$	
Non-cash unrealized gain (loss) on marketable securities	$	(128)	$	4,047
Issuance of common stock in connection with the grant of stock	$	41	$	

The accompanying notes are an integral part of these condensed consolidated financial statements.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES
UNAUDITED NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS

1. Formation and Business of the Company

We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted molecular therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using tumor suppressors, cytokines and other targeted molecular therapies. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells, stimulate immune activity and enhance conventional cancer therapies.

We have not yet generated any significant revenue from unaffiliated third parties, nor is there any assurance of future product revenue. We earn minimal revenue from contract services activities, interest income, and rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. We do not expect to generate revenue from the commercial sale of our products in the near future. We may never generate revenue from the commercial sale of our products.

Our research and development activities involve a high degree of risk and uncertainty. Our ability to successfully develop, manufacture and market our proprietary products is dependent upon many factors. These factors include, but are not limited to, the need for and the ability to obtain additional financing, the reliance on collaborative research and development arrangements with corporate and academic affiliates and the ability to develop manufacturing, sales and marketing experience. Additional factors include uncertainties as to patents and proprietary technologies, competitive technologies, technological change and risk of obsolescence, development of products, competition, government regulations and regulatory approval, and product liability exposure. As a result of these factors and the related uncertainties, there can be no assurance of our future success.

2. Basis of Presentation and Significant Accounting Policies

The accompanying condensed consolidated financial statements have been prepared in accordance with United States generally accepted accounting principles (GAAP) for interim financial information and pursuant to the rules and regulations of the Securities and Exchange Commission (SEC). These financial statements do not include all of the information and footnotes required under GAAP for complete financial statements. In management s opinion, all accounting entries considered necessary for a fair presentation have been made in preparing these financial statements, and such entries are normal in nature. Operating results for the three month period ended March 31, 2007 are not necessarily indicative of the results that may be expected for the entire fiscal year.

Our significant accounting policies are described in Note 2 to the Consolidated Financial Statements included in our Annual Report on Form 10-K for the year ended December 31, 2006, filed with the SEC on March 8, 2007.

We account for our investment in Introgen Research Institute, Inc. (IRI) in accordance with FIN 46(R), Consolidation of Variable Interest Entities (as amended). Accordingly, the accounts of IRI are included in these consolidated financial statements. We record a non-controlling interest relative to the portion of IRI we do not own.

See footnote 6 below regarding our adoption of and accounting policies related to Statement of Financial Accounting Standard (SFAS) Interpretation No. 48, Accounting for Uncertainty in Income Taxes an interpretation of SFAS Statement No. 109 (FIN 48),

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3. Introgen Research Institute, Inc.

During the three months ended March 31, 2007, we purchased 49% of the outstanding stock of Introgen Research Institute, Inc. for $10,000. The other 51% of IRI is owned by our corporate Secretary, who is also an Introgen shareholder. We transferred to IRI an NIH grant originally awarded to us. IRI will be responsible for the remaining research contemplated by that grant and will receive future funding, if any, from the NIH under that grant. For the three months ended March 31, 2007, we recorded grant income of $213,000 related to grants held by IRI. We have contractual relationships with IRI under which we may perform research and development services for them in the future.

4. Stockholders Equity

Under an agreement with us, Aventis Pharmaceutical Products, Inc. (Aventis), which is now Sanofi-Aventis, must vote all of its Introgen shares in the same manner as the shares voted by a majority of the other stockholders on any corporate action put to a vote of our stockholders. This voting requirement terminates at the earliest of June 2011 or the sale of these shares pursuant to an effective registration statement on the open market or to an Aventis non-affiliate, as defined in the voting agreement. As of December 31, 2006, Aventis reported owning approximately 1.8 million shares of our common stock that are subject to the voting agreement.

5. Accumulated Other Comprehensive Income or Loss

Accumulated other comprehensive income or loss is included as a component of stockholders equity and is composed of (1) foreign currency translation adjustments and (2) unrealized gains and losses on investments designated as available-for-sale securities. Accumulated other comprehensive income (loss) is calculated as follows (in thousands):

	Three Months Ended March 31	
	2006	**2007**
Net loss	$ (8,219)	$ (5,617)
Foreign currency translation adjustments		(4)
Unrealized gain (loss) on marketable securities	(128)	4,047
Total comprehensive loss	$ (8,347)	$ (1,574)

6. Accounting for Uncertainty in Income Taxes

We adopted FIN 48 as of January 1, 2007. FIN 48 applies to all tax positions accounted for under SFAS No. 109. FIN 48 refers to tax positions as positions taken in a previously filed tax return or positions expected to be taken in a future tax return which are reflected in measuring current or deferred income tax assets and liabilities reported in the financial statements. FIN 48 further clarifies a tax position to include, but not be limited to, the following:

An allocation or a shift of income between taxing jurisdictions;

The characterization of income or a decision to exclude reporting taxable income in a tax return;

A decision to classify a transaction, entity, or other position in a tax return as tax exempt.

FIN 48 provides that a tax benefit may be reflected in the financial statements only if it is more likely than not that a company will be able to sustain the tax return position, based on its technical merits. If a tax benefit meets this criterion, it should be measured and recognized based on the largest amount of benefit that is cumulatively greater than 50% likely to be realized. This approach is a change from previous practice under which a tax benefit could be recognized only if it was probable a tax position could be sustained.

FIN 48 requires we make qualitative and quantitative disclosures, including a discussion of reasonably possible changes that might occur in unrecognized tax benefits over the next twelve months, a description of open tax years by major jurisdictions and a roll-forward of all unrecognized tax benefits, presented as a reconciliation of the beginning and ending balances of the unrecognized tax benefits on an aggregated basis.

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The Company and certain of its subsidiaries file income tax returns in the U.S. federal jurisdiction, various state jurisdictions, and certain foreign jurisdictions. Generally, the Company is no longer subject to examinations for U.S. federal income taxes for years prior to 2003 and for state income taxes for years prior to 2002. Examinations for foreign income taxes for previous years remain open, but tax considerations in those jurisdictions are not material to us.

The adoption of FIN 48 did not have a material impact on our financial statements or disclosures. As of January 1, 2007 and March 31, 2007, we did not recognize any assets or liabilities for unrecognized tax benefits relative to uncertain tax positions. We anticipate no significant increase or decrease to gross unrecognized tax benefits will be recorded during the next twelve months. Any interest or penalties resulting from examinations will continue to be recognized as a component of the income tax provision. However, since there are no unrecognized tax benefits as a result of tax positions taken, we have no accrued interest and penalties.

7. Subsequent Event

Subsequent to March 31, 2007, we were relieved of the need to pay certain invoices that were recorded as accounts payable and expensed in earlier periods. We recorded this event as of March 31, 2007, which reduced our research and development expense by approximately $1.1 million for the three months ended March 31, 2007.

Item 2. Management s Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis should be read in conjunction with our condensed consolidated financial statements and the related notes thereto included in this Quarterly Report on Form 10-Q and the other documents we have filed with the Securities and Exchange Commission. In addition to historical information, this report and the following discussion and analysis contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. These statements address our future operations, financial condition, business strategies and other prospective items and include, among other subjects, matters concerning our expectations regarding:

- The growth of our operations, business and revenues and the growth rate of our costs and expenses;
- Future increases in our research and development, sales and marketing and general and administrative expenses;
- The sufficiency of our existing cash, cash equivalents, marketable securities and cash generated from operations;
- Our expectations regarding various regulatory applications, procedures and approvals relating to our product candidates, including but not limited to our expectations regarding the timing of such applications, procedures and approvals;
- Better efficacy of our product candidates through the use of biomarkers ; and
- Application of our research and development expertise to other diseases that result from cellular dysfunction and uncontrolled cell growth.

The words believe, expect, anticipate and other similar expressions generally identify forward-looking statements. These forward-looking statements are based on our current expectations and entail various risks and uncertainties. Given these risks and uncertainties, readers are cautioned not to place undue reliance on such forward-looking statements. We undertake no obligation to revise or publicly release the results of any revision to these forward-looking statements. These forward-looking statements are subject to certain risks and uncertainties that could cause our actual results to differ materially from those reflected in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report, and in particular, the risks discussed under the heading Risk Factors in Part II, Item 1A of this report and those discussed in other documents we file with the Securities and Exchange Commission.

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Overview

Introgen Therapeutics, Inc. was incorporated in Delaware in 1993. We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted molecular therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using tumor suppressors, cytokines and other targeted molecular therapies. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells, stimulate immune activity and enhance conventional cancer therapies.

Our primary approach to the treatment of cancers is to deliver targeted molecular therapies that increase production of normal cancer-fighting proteins to induce apoptosis, cell cycle control, cell growth control and gene regulation, including the regulation of angiogenic and immune factors. Our products work by acting as templates for the transient *in vivo* production of proteins that have pharmacological properties. The resultant proteins engage disease-related molecular targets or receptors to produce specific therapeutic effects.

We believe the use of targeted molecular therapies to induce the production of biopharmaceutical proteins represents a new approach for treating many cancers while avoiding the toxic side effects common to traditional therapies. We have developed significant expertise in developing targeted therapies that may be used to treat disease and in using what we believe are safe and effective delivery systems to transport these agents to the cancer cells. We believe we will be able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

Our lead product candidate, ADVEXIN® therapy, combines the p53 tumor suppressor with a non-replicating, non-integrating, adenoviral delivery system we have developed and extensively tested. The p53 molecule is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer growth and protect cells from becoming cancerous. We are developing other product candidates for the treatment of cancer using other molecules and delivery systems, such as the mda-7 and FUS1 tumor suppressors.

We believe our research and development expertise gained from our targeted molecular therapies for cancer is also applicable to other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. As a result, we are conducting research in collaboration with medical institutions to understand the safety and effectiveness of our targeted molecular therapy product candidates in the treatment of other diseases.

We typically license the technologies on which our products are based from third parties. These licenses generally grant us exclusive rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of product candidates based on those technologies.

Our product research and development efforts include pre-clinical activities as well as the conduct of Phase 1, 2 and 3 clinical trials. We rely on third parties to treat patients in their facilities under these clinical trials. We produce ADVEXIN therapy and other product candidates in manufacturing facilities we own and operate using production methods we developed. We hold a number of patents or patents pending on certain product candidates and manufacturing processes used to produce certain product candidates.

We have not yet generated any significant revenue from unaffiliated third parties, nor is there any assurance of future product revenue. We earn minimal revenue from contract services activities, grants and interest income, as well as rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. We do not expect to generate revenue from the commercial sale of our products in the near future. We may never generate revenue from the commercial sale of our products.

Our principal executive offices are located at 301 Congress Avenue, Suite 1850, Austin, Texas 78701. Our telephone number is (512) 708-9310. Our Internet website address is www.introgen.com.

The Introgen Approach

Our primary approach for the treatment of cancers is to deliver targeted molecular therapies that increase production of normal cancer-fighting proteins. The resultant proteins engage disease-related molecular targets or receptors to produce specific therapeutic effects. We believe we are able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

Most cancers are amenable to local treatment, such as surgery and radiation, which are administered far more often than systemic cancer treatments. Our locally delivered product candidates, such as ADVEXIN therapy and INGN 241, IL24 therapy, deposit

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therapeutic molecules directly into a patient s cancerous tumor by hypodermic syringe. We have systemic formulations for intravenous use in those cases for which a systemic therapy may be indicated and have applied ADVEXIN therapy using a nanoparticle formulation system to deliver our tumor suppressors.

We initially focused on advanced cancers lacking effective treatments and in which local tumor growth control, where the tumor stops growing or shrinks, is likely to lead to measurable benefit. We have expanded our focus to include earlier stage cancers and pre-malignancies. We believe our clinical trials have shown that our therapies can be used alone and in combination with conventional treatments such as surgery, radiation therapy and chemotherapy.

The Introgen Strategy

Our objective is to be a leader in the development of targeted molecular tumor suppressor therapies and other products for the treatment of cancer and other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. To accomplish this objective, we are pursuing the following strategies:

Develop and Commercialize ADVEXIN Therapy, INGN 241 and INGN 401 for Multiple Cancer Indications. We plan to continue our development programs to commercialize our ADVEXIN therapy, using the p53 tumor suppressor, our INGN 241 product, using the mda-7 tumor suppressor, also know as interleukin 24 (IL-24), and our INGN 401 product, using the FUS1 tumor suppressor, in multiple cancer indications.

Develop Our Portfolio of Targeted Molecular Therapies and Other Drug Products. Utilizing our research, clinical, regulatory and manufacturing expertise, we are evaluating development of additional molecular therapies for various cancers, including:

INGN 225, a highly specific cancer immunotherapy;

INGN 234, an oral rinse or mouthwash formulation containing the p53 tumor suppressor;

INGN 402 and 403, using nanoparticle formulations for systemic delivery of the p53 and mda-7 tumor suppressors; and

INGN 007, a replication-competent viral therapy.

We have an established process for evaluating new drug candidates and advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate. We intend to evaluate additional opportunities to in-license or acquire new technologies.

Develop a Nanoparticle Systemic Administration Platform. Early pre-clinical and clinical studies with these new nanoparticle drugs have demonstrated a good safety profile and promising anti-cancer activity. In addition to FUS-1, we incorporate the p53 tumor suppressor and the mda-7 tumor suppressor in these nanoparticle formulations. We also have in-licensed technologies for nanoparticle delivery of DNA, siRNA, proteins, peptides and polypeptides.

Develop the Topical Use of Tumor Suppressors. We plan to continue developing topical product candidates for the treatment or prevention of oral and dermal cancers, specifically INGN 234 referred to above. We believe these treatments are a logical extension of our loco-regional delivery of cancer therapies and represent attractive product candidates since pre-malignant and malignant cells can be exposed to natural, biological tumor suppressors and DNA repairing agents.

Establish Targeted Sales and Marketing Capabilities. The oncology market can be effectively addressed by a small, focused sales force because it is characterized by a concentration of specialists in relatively few major cancer centers. We believe we can address this market by a combination of building a direct sales force as part of the ADVEXIN therapy commercialization process and pursuing marketing and distribution agreements with corporate partners for ADVEXIN therapy as well as additional products.

Expand Our Market Focus to Non-Cancer Indications. We plan to leverage our scientific, research and process competencies in

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molecular therapy and vector development to pursue targeted molecular therapies for a variety of other diseases and conditions. We believe these therapies could hold promise for diseases such as cardiovascular disease and rheumatoid arthritis, which, like cancer, result from cellular dysfunction or uncontrolled cell growth.

Product Development Overview

ADVEXIN® Therapy (p53)

ADVEXIN Therapy Overview and Regulatory Status

Our lead product candidate, ADVEXIN® therapy, combines the p53 tumor suppressor with a non-replicating, non-integrating adenoviral delivery system we have developed and extensively tested. The p53 molecule is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

ADVEXIN therapy for head and neck cancer has been designated an Orphan Drug under the Orphan Drug Act. This designation may give us up to seven years of marketing exclusivity for ADVEXIN therapy for this indication if approved by the U.S. Food and Drug Administration (FDA). The European Medicines Agency (EMEA) Committee for Orphan Medicinal Products has granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of Li-Fraumeni Syndrome. This designation has been ratified by the European Commission. Li-Fraumeni Syndrome is an inherited cancer characterized by inherited mutations in the p53 tumor suppressor gene. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a 10-year period of marketing exclusivity from the date of approval.

We have an agreement with EMEA to file for marketing approval for ADVEXIN therapy under the EMEA s Exceptional Circumstances (EC) provisions. The application will be for the use of ADVEXIN therapy for the treatment of Li-Fraumeni Syndrome. Exceptional circumstances provisions are designed to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMEA under these provisions can be reviewed on an expedited basis. This EC registration approach is designed by EMEA to be more streamlined than EMEA s Conditional Approval procedures, which are similar to the FDA s Accelerated Approval regulations.

As a result of an audit and inspection by a European Union Qualified Person (QP), we are certified with the United Kingdom s Medicines and Healthcare Products Regulatory Agency (MHRA) that our facilities and production processes are compliant with European Good Manufacturing Practices for the manufacture of ADVEXIN therapy. The MHRA is the competent authority in the United Kingdom and is a component of the EMEA.

We have two ongoing Phase 3 clinical trials of ADVEXIN therapy in patients with advanced recurrent squamous cell carcinoma of the head and neck (recurrent head and neck cancer). These trials involve administration of ADVEXIN therapy, both independently and in combination with chemotherapy, in recurrent head and neck cancer.

We received Fast Track designation for ADVEXIN therapy from the FDA under its protocol assessment program as a result of the FDA s agreement with the design of our two ongoing Phase 3 clinical trials of ADVEXIN therapy. Under this Fast Track designation, the FDA will take actions to expedite the evaluation and review of the Biologics License Application (BLA) for ADVEXIN therapy. We plan to pursue with the FDA an Accelerated Approval of ADVEXIN therapy, which is one alternative provided under a Fast Track designation.

We reviewed historically successful FDA registration strategies for numerous cancer drugs, noting that during the past decade, approximately 14 cancer drugs were initially approved based upon submissions of Phase 2 clinical data. A number of the Phase 2 trials supporting these approvals employed single-arm studies involving relatively small patient populations. Virtually all of those drugs relied on surrogate endpoints for approval and a substantial number of the products were for orphan drug indications.

We conducted a series of meetings with the FDA to develop and implement the filing strategy for the BLA for ADVEXIN therapy, which is the application for approval to market and sell ADVEXIN therapy in the United States. As a result of these meetings, we are developing and pursuing an initial rolling BLA filing strategy based on data from our Phase 2 and Phase 3 clinical trials of ADVEXIN

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therapy for treatment of recurrent head and neck cancer. The FDA has concurred that preliminary evaluation of this data suggests a level of efficacy consistent with the standard for the initiation of a rolling BLA (a submission process also known as Submission Of a Partial Application or SOPA). The FDA has also concluded that ADVEXIN therapy continues to show promise with respect to an unmet medical need since there are limited treatment alternatives in the United States for recurrent head and neck cancer. The FDA has also concluded that the clinical development program for ADVEXIN therapy for recurrent head and neck cancer continues to meet the criteria for Fast Track designation. In conjunction with the new data, the new analyses, and other newly employed biological techniques, we hope to more specifically target recurrent head and neck cancer in patients using indicators known as biomarkers , as discussed further below. We believe this approach will improve efficacy by identifying the patients most likely to benefit from Advexin therapy.

We submitted a SOPA Request to the FDA Division of Cellular and Gene Therapies proposing a rolling BLA for ADVEXIN therapy for the treatment of recurrent head and neck cancer, based primarily on data from our Phase 2 clinical trials. We have proposed to the FDA that, since the basis of the proposed rolling BLA is Phase 2 clinical data utilizing surrogate endpoints, the rolling BLA could be evaluated under the provisions of Subpart H for Accelerated Approval. In order to fully explore all of the review and approval possibilities for ADVEXIN therapy, the FDA has requested we submit new data and analyses from the Phase 2 ADVEXIN therapy clinical trials for recurrent head and neck cancer and conduct efficacy analyses on one or both of our ongoing Phase 3 trials. Given that we have two ongoing Phase 3 clinical trials in recurrent head and neck cancer as discussed further below, we and the FDA are evaluating the most effective use of the data from these Phase 2 and 3 clinical trials in the review and approval of ADVEXIN therapy. Regulatory approval approaches may allow Accelerated Approval on the basis of Phase 2 clinical data with subsequent confirmatory data being provided by the Phase 3 clinical studies or, alternatively, a full approval based on data from Phase 2 and certain Phase 3 clinical trials. We have reached agreement with the FDA that biomarker evaluations as described in its recently announced Critical Path Initiative, which permits new product evaluation on the basis of specifically targeted (i.e., by prognostic or biologic parameters) clinical trials and/or patient populations, can be used in the ADVEXIN therapy approval process. This initiative also encouraged sponsors to examine novel approaches to define tumor responses that correlate with clinical benefit. We have employed several biomarker and response criteria to evaluate ADVEXIN efficiency as described below.

We have initiated the efficacy analysis of our ADVEXIN Phase 3 study. This analysis will involve comparing ADVEXIN therapy to methotrexate for the treatment of recurrent head and neck cancer. The prospective efficacy assessment of the randomized, controlled clinical trial is based upon analysis of biomarkers and clinical outcomes. The efficacy evaluation of the Phase 3 study will incorporate the biomarker analyses identified in Phase 2 clinical trials of ADVEXIN therapy of recurrent head and neck cancer. The Phase 3 Statistical Analysis Plan was finalized with input from the FDA. Introgen has followed advice from the FDA to accelerate its Phase 3 safety analysis and to perform an efficacy analysis for this study. An independent Data Safety Monitory Board review in 2006 noted no safety issues with the Phase 3 study.

During 2007, we plan to complete the efficacy analyses of one or both of our two ongoing Phase 3 clinical trials for recurrent head and neck cancer, submit Phase 2 and Phase 3 clinical data to the FDA and EMEA in support of our ADVEXIN registration program and complete filings with the EMEA in support of an Exceptional Circumstance Approval Application for Li-Fraumeni Syndrome cancers that are due to inherited abnormalities in the p53 tumor suppressor gene that is the molecular target of ADVEXIN therapy.

We cannot assure you that we will be able to achieve these regulatory milestones during the time period that we currently anticipate. We may encounter delays in the regulatory process relating to these milestones due to additional information requirements from regulatory authorities, unintentional omissions in our applications, additional government regulation or other delays in the review process. We may update our expectations regarding these regulatory milestones from time to time to reflect new information as it becomes available to us.

ADVEXIN Therapy as a Targeted Molecular Therapy

We identified a set of predictive indicators, commonly referred to as biomarkers, associated with high response rates and increased survival in Phase 2 clinical trials of ADVEXIN therapy in patients with recurrent head and neck cancer. These trials are discussed in more detail below under Other ADVEXIN Therapy Activities. These biomarkers

support the use of ADVEXIN therapy as a targeted molecular therapy.

The FDA, the National Cancer Institute (NCI), and the Centers for Medicare & Medicaid Services are undertaking the Oncology Biomarker Qualification Initiative to expedite the development of novel cancer treatments. These agencies define biomarkers as

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clinical or biological indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, laboratory tests on blood or tissue samples as well as by clinically defined parameters. This initiative was developed to employ biomarkers as a way of speeding the development and evaluation of new cancer therapies.

The identification of predictive indicators of ADVEXIN therapy activity is responsive to these initiatives by predicting the patient populations most likely to benefit from a specific cancer therapy. The population we identified as benefiting from ADVEXIN therapy includes patients who are less likely to respond to standard therapies such as chemotherapies and radiation.

A molecular biomarker predictive of ADVEXIN therapy activity is abnormal p53 function detected in tumor tissues by a routine immunohistochemistry laboratory test. In patients with the abnormal p53 biomarker, ADVEXIN therapy caused a statistically significant increase in median survival of 11.6 months compared to only 3.5 months for patients without abnormal p53 function. Patients with abnormal p53 function are known to have a poor prognosis when treated with standard therapies. In addition to this molecular biomarker, we have identified clinical prognostic biomarkers that correlate with statistically significant increases in survival, partial and complete tumor responses and durable locoregional disease control (tumor responses or tumor growth arrest for two months or longer in duration) following treatment with ADVEXIN therapy. These clinical biomarkers include prior chemotherapy consistent with ADVEXIN therapy s mechanism of action of inducing tumor death in cells, or apoptosis, with DNA damage from previous treatments.

The predictive biomarkers define target populations of patients with higher tumor response rates and increased survival following treatment with ADVEXIN therapy. In an analysis of 112 patients treated in the Phase 2 trial of recurrent head and neck cancer treated with the ADVEXIN therapy dose (high dose) proposed for regulatory approval, we identified clinical prognostic biomarkers that correlate with statistically significant increases in survival, partial and complete tumor responses and durable locoregional disease control (tumor responses or tumor growth arrest for two months or longer in duration) following treatment with ADVEXIN therapy. These clinical biomarkers include prior chemotherapy consistent with ADVEXIN therapy s mechanism of action of inducing death in tumor cells with DNA damage from previous treatments. Depending on the tumor response criteria and clinical biomarkers selected to define sub-populations, tumor responses in over 33% of the patients were observed. In addition, patients who achieved tumor responses defined by a greater than 50% reduction in tumor size had a median survival of approximately 40 months. Spontaneous tumor remissions generally are not observed in recurrent head and neck cancer. This median survival of over three years for these ADVEXIN therapy responders compares favorably with the approximate six month survival time typically expected for recurrent head and neck cancer patients who have failed prior therapies.

The targeted molecular therapy provided by ADVEXIN therapy is evidenced by its use to successfully treat a Li-Fraumeni Syndrome cancer patient on a compassionate use basis under a protocol authorized by the FDA. Li-Fraumeni Syndrome cancer patients have inherited defects in the p53 tumor suppressor gene that is the target of ADVEXIN therapy. Our treatment of a tumor in a Li-Fraumeni Syndrome patient with ADVEXIN therapy led to improvement of tumor-related symptoms and resulted in a complete response in the treated lesion as determined by positron emission tomography (PET) computerized tomography (CT) scans. PET-CT scans measure the metabolic activity of tumors and are being increasingly utilized in the management of cancer patients because they provide more sensitive assessments of treatment effects compared to conventional CT and magnetic resonance imaging scans.

This Li-Fraumeni Syndrome study defined important biomarkers to guide the administration of ADVEXIN therapy to patients with other cancers who display p53 pathway abnormalities. Our molecular analysis of biopsies of the Li-Fraumeni Syndrome tumor before and after treatment identified key markers of p53 pathway abnormalities that are used to predict and evaluate the effects of ADVEXIN therapy. These markers included detection of abnormal levels of p53 protein that identify aberrant p53 pathways and the induction of molecular markers of tumor growth control and tumor cell death that validate ADVEXIN therapy s mechanisms of action. We believe these biomarkers can be used to identify patients most likely to benefit from ADVEXIN therapy.

The EMEA Committee for Orphan Medicinal Products has granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of Li-Fraumeni Syndrome. This designation has been ratified by the European Commission. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a 10-year period of

marketing exclusivity from the date of approval. We received this designation through Gendux AB, our wholly-owned subsidiary.

We have an agreement with EMEA to file for marketing approval for ADVEXIN therapy under the EMEA s Exceptional Circumstances provisions. The application will be for the use of ADVEXIN therapy for the treatment of Li-Fraumeni Syndrome.

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Exceptional circumstances provisions are designed by EMEA to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMEA under these provisions can be reviewed on an expedited basis. This registration approach is more streamlined than EMEA s Conditional Approval procedures, which are similar to the FDA s Accelerated Approval regulations. As a result of the encouraging clinical findings in treating Li-Fraumeni Syndrome, we have made ADVEXIN therapy available on a compassionate use basis to qualified Li-Fraumeni Syndrome patients with tumors refractory to standard treatment.

Li-Fraumeni Syndrome is an inherited genetic disorder that greatly increases the risk of developing several types of cancer typically with initial occurrence at a young age. The majority of Li-Fraumeni Syndrome families have inherited mutations in the p53 tumor suppressor gene. The findings described above have been presented at the annual meetings of the American Society of Gene Therapy (ASGT) and the American Society of Clinical Oncology (ASCO).

Other ADVEXIN Therapy Activities

We performed a Phase 2 clinical trial of ADVEXIN therapy combined with neoadjuvant chemotherapy and surgery in women with locally advanced breast cancer. The results of this study were published in the journal *Cancer.* Objective clinical responses were seen following the combined therapy in 100% of the patients with a median of 80% reduction in tumor size. Following tumor shrinkage, complete tumor removal by subsequent surgery was achieved in 100% of the patients. At a median follow-up of 37 months (range, 30-41 months), four patients (30%) developed systemic recurrence and two patients died. The estimate breast cancer-specific survival rate at three years was 84%. There was no increase in systemic toxicity. Neoadjuvant treatments are administered prior to surgery and represent a novel and increasingly applied approach to making surgical tumor resections less invasive, improving outcomes and facilitating breast conservation.

We completed a Phase 2 clinical trial of ADVEXIN therapy administered as a complement to radiation therapy in non-small cell lung cancer. In the 19 patients who participated in the trial, combined ADVEXIN therapy and radiation treatment resulted in 63% biopsy-proven complete responses at three months, which is approximately four times the expected rate using radiotherapy alone. The results of this study were published in *Clinical Cancer Research.*

We performed a Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced, unresectable, squamous cell esophageal cancer. Results of this trial in patients with esophageal cancer refractory to chemotherapy and radiation indicate three of the ten patients treated, or 30%, had negative biopsies after receiving ADVEXIN therapy. The median survival of the patients treated with ADVEXIN therapy was approximately twelve months, which compared favorably to historical controls in which a median survival of less than ten months was observed for patients who did not respond to standard treatments. Six patients, or 60%, were still alive one year after beginning ADVEXIN therapy. This clinical trial was performed at Chiba University in Japan.

We have completed other clinical trials of ADVEXIN therapy, including Phase 1 studies in prostate cancer and bronchoalveolar carcinoma. To date, clinical investigators at sites in North America, Europe and Japan have treated over 600 patients with ADVEXIN therapy, establishing a large safety database. Findings from several of our clinical trials have been published in *Clinical Cancer Research* and *Proceedings of the American Society for Clinical Oncology* as well as presented at numerous conferences, including the San Antonio Breast Cancer Conference and various meetings of the ASCO, ASGT and the American Association for Cancer Research.

A growing body of data suggests ADVEXIN therapy demonstrates clinical activity in a variety of cancer indications. Safety data from our clinical trials suggest this activity may be achieved without the treatment-limiting side effects frequently associated with many other cancer therapies.

Our clinical trials indicate ADVEXIN therapy is well tolerated as a monotherapy. The addition of ADVEXIN therapy to standard chemotherapy, surgery or radiation does not appear to increase the frequency or severity of side effects normally associated with these treatment regimens.

Recent studies provide new insight into the molecular pathways by which the p53 tumor suppressor, the active component of ADVEXIN therapy, kills tumor cells. These studies were undertaken to provide additional molecular data supporting the activity observed during the clinical development of ADVEXIN therapy and to provide additional information regarding the specific pathways that mediate the observed clinical effects of ADVEXIN therapy. The studies were conducted by our collaborators at Okayama

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University in Japan and at The University of Texas M. D. Anderson Cancer Center and were published in *Molecular Cancer Therapeutics.*

Other data suggest the enhanced therapeutic effects of a combination of ADVEXIN and Erbitux® therapies in an animal model of human non-small cell lung cancer. Other pre-clinical studies conducted by our collaborators at Wayne State University, the Karmanos Cancer Institute located in Detroit, Michigan and the University of California-Irvine, as published in *The Laryngoscope*, show that the combination of ADVEXIN therapy and docetaxel resulted in increased levels of programmed cell death in head and neck tumor cells.

We hold a worldwide, exclusive license to a family of patent applications directed to combination therapy using ADVEXIN therapy with inhibitors of epidermal growth factor receptors (EGFr inhibitors) such as Erbitux®, Vectibix®, Tarceva® and Iressa®. We licensed this family of patents from M. D. Anderson Cancer Center. This important technology is based on the discovery by scientists at M. D. Anderson Cancer Center that p53 therapies (which is the basis for our ADVEXIN therapy) and mda7 therapies (which is the basis for our INGN 241 product candidate discussed below) can work synergistically with inhibitors of epidermal growth factor receptors to arrest tumor growth. Preclinical studies have shown that this therapeutic approach results in a greater level of cancer cell death than when either therapy is used alone.

We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN therapy.

INGN 241 (mda-7)

INGN 241 uses mda-7, a promising tumor suppressor, that we believe, like p53, has broad potential to induce apoptosis or cell death in many types of cancer. We have combined the mda-7 tumor suppressor with our adenoviral delivery system to form INGN 241. Our pre-clinical trials have shown the protein produced by INGN 241 suppresses the growth of many cancer cells, including those of the breast, lung, ovaries, colon, prostate and the central nervous system, while not affecting the growth of normal cells. Because INGN 241 kills cancer cells even if other tumor suppressors, including p53, are not functioning properly, it appears mda-7 functions via a novel mechanism of tumor suppression.

We have completed a Phase 1/early Phase 2 clinical trial using INGN 241 to evaluate safety, mechanism of action and efficacy in approximately 25 patients with solid tumors. This trial indicated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated with its use. We are conducting later stage clinical trials using INGN 241 in patients with metastatic melanoma. We are conducting a Phase 3 clinical trial using INGN 241 in combination with radiation therapy for solid tumors. We are currently designing a pivotal, clinical trial for INGN 241 combined with bevacizumab.

Data from our Phase 1 trial of INGN 241 in patients with solid tumors demonstrate that direct injection of INGN 241 induced programmed cell death in 100% of the tumors treated, even in patients who had failed prior therapy with other anti-cancer drugs. Clinical responses were observed in 44% of the treated lesions, including complete and partial responses in two patients with melanoma. Patients treated with INGN 241 had increases in a subset of T-cells that help to destroy cancer cells, which is consistent with the role of the mda-7 protein as a member of the interleukin family of immune stimulating proteins.

We have conducted pre-clinical work indicating that in addition to its known activity as a tumor suppressor, the protein produced by mda-7 may also stimulate the body s immune system to kill metastatic tumor cells and to protect the body against cancer, thereby offering the potential of providing an added advantage in treating various cancers because it may attack cancer using two different mechanisms. Because the mda-7 tumor suppressor may act as a cytokine, or immune system modulator, it is also known as interleukin 24, or IL-24. The mda-7 molecule may also work as a radiation sensitizer to make several types of human cancer cells more susceptible to radiation therapy. We have seen evidence of this effect in pre-clinical and clinical settings.

We have identified the molecular pathways by which mda-7, the active component of INGN 241, induces growth arrest and programmed cell death or apoptosis in cancer cells. Pre-clinical studies using lung cancer cells have demonstrated the mda-7 protein binds to a critical cellular enzyme known as PKR. The binding of mda-7 to PKR is essential for the anti-cancer activity of INGN 241. The identification of this binding partner demonstrates a significant advancement in understanding how this therapeutic can be effective against cancer. Additional studies have identified

bystander killing of pancreatic cancer cells by the mda-7 protein. Bystander killing involves the killing of neighboring tumor cells by the mda-7 protein released from adjacent INGN 241-treated tumor cells.

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Pre-clinical data indicate INGN 241 works synergistically with celecoxib, marketed by Pfizer as Celebrex®, to inhibit the growth and increase killing of breast cancer cells. The combination of celecoxib and INGN 241 showed greater than additive increases in cell death compared with either therapy alone and also resulted in the suppression of tumor cell growth.

Pre-clinical data indicate INGN 241 and bevacizumab, marketed by Roche Holding AG and Genentech, Inc. (Genentech) as Avastin®, each inhibit tumor angiogenesis through distinct mechanisms in models of lung cancer. Study results demonstrate that the combination of INGN 241 and Avastin® significantly increases anti-tumor activity compared with either agent used separately. We have observed synergistic acti