

Sender: Wheeler William </O=CARTER-WALLACE/OU=CRANMAIL/CN=RECIPIENTS/CN=EXCHANGE/CN=WWHEELER>
Sent: Wednesday, October 30, 2002 6:47:59 PM
Recipient: Klein Barbara <BKlein@medpointeinc.com>
Subject: Life Cycle Management Astelin Projects
Attachments: Life Cycle Management Astelin Projects

Barabara: here's the LCM document for distribution. Thanks, Bill
Life Cycle Management Astelin Projects



ASTELIN[®] NASAL SPRAY

LIFE CYCLE MANAGEMENT PROJECTS

(Preliminary Plan)

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PACKAGING CONFIGURATION PROJECTS

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Product: ASTELIN NASAL SPRAY

Project: Pediatric Packaging

Objective: To develop a new Astelin Nasal Spray packaging configuration that will be designated as “Pediatric” containing a single 17mL flat bottom bottle and a single current VP3 Valois pump.

Background: FDA approval has been obtained for the use of Astelin Nasal Spray in children 5 to 11 years of age. The current packaging configuration provides twice the product volume for pediatric patients, compared to adults (based on the differences in dose). Therefore, rather than 2 x 17mL bottles and one pump provided in an adult trade carton, one 17mL bottle and one pump will be provided in a pediatric trade carton. Development of this pediatric package involves labeling revisions to the following: package insert, patient instructions, 17mL bottle label, trade carton.

Feasibility: High

Likelihood of Success: High.

Time: There are three possible scenarios which would affect timing:

(1) Annual Reportable Change: internal revision of the product labeling to simply remove all references to two 17mL bottles and any artwork geared toward adults, making no reference to a “Pediatric Package”. This change could be implemented as soon as final printed labeling (FPL) is available and would only require notification to FDA in the subsequent NDA Annual Report.

(2) Changes Being Effectuated (CBE) Supplement or Annual Reportable: internal revision of the labeling to remove all references to two 17mL bottles and include a reference to “Pediatric Package” and artwork geared toward children on the bottle and/or carton regarding “Pediatric Package”. Depending upon the extent of the pediatric package marketing spin (to be evaluated by Regulatory), this change could either be handled as indicated in 1) above, or it would require the submission of a CBE. For the CBE, draft labeling would be submitted in a supplement which could be implemented after 30 days, unless FDA objected.

(3) CBE or Prior Approval Supplement (PAS): in addition to internal labeling changes to remove all references to two 17mL bottles, addition of artwork geared toward children and indication of “Pediatric Package”, if a value added piece (to be evaluated by Regulatory) is to be included, submission of a CBE or PAS would be required. FDA approval (PAS) would be required in almost any case of the use of value added material.

Cost: A cost of approximately \$1000.00 per individual piece of product labeling will be incurred. Total cost approximately \$5000.00. Cost for destruction of existing label inventory TBD.

Milestones/Go no Go Decisions:

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Resolution of the issues concerning the Sepracor contract	TBD	TBD
Determination of the changes to be incorporated	TBD	TBD
Determination of short vs long-term use of pediatric package*	TBD	TBD
Determination of FDA submission requirements	BD	TBD
Initiation of internal approval process for labeling components	1-2 weeks	TBD
Completion of labeling approval process	2-3 weeks	TBD
Submission to FDA	TBD	TBD
Launch	TBD	TBD

Promotability: Labeling change could be used to support safety and convenience/cost savings in pediatric patients.

Market Forecast:

* Based upon recent market “models”. Links into life cycle for V-bottom bottle configuration.

Product: ASTELIN NASAL SPRAY

Project: V-Bottom Bottle/Cap Configuration-Trade (30.0 mL)

Objective: To provide a back-up for the currently approved v-bottom bottle/pump configuration in the event that the manufacturability of the bottle/pump configuration is not achievable either from an engineering or specification standpoint.

Background: Historically the 17mL Owens Brockway flat bottom bottle/cap configuration has not been associated with high particulate levels. The V-bottom bottle has had higher particulate levels. Data has also demonstrated that the placement of a spigot ring pump on a V-bottom bottom at release introduces a significant level of particulates that could potentially be outside the current specifications. These data again suggest that the major source of particulates is from the pump and efforts would need to be initiated to reduce the associated particulates.

Feasibility: The feasibility of this configuration will depend on obtaining a suitable cap and future studies to determine the particulate levels when the cap is mechanically placed on the V-bottom bottle.

Likelihood of Success: High. If the particulate level from the pump component can be significantly reduced and the mechanical placement of the pump cannot be achieved, then this configuration would be a suitable back-up. Otherwise this project could potentially have the same particulate issues as the bottle/cap configuration.

Time: 18-28 months from the acquisition of suitable packaging components

Cost: Milestones/Go no Go Decisions:...

Feasibility	3 months	\$17,500
Stability (Decatur)	12 months	\$35,000
FDA Submission	3 months	
FDA Approval	6-9 months	

Promotability: New package configuration will be fully promotable.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: V-Bottom Bottle/Pump Configuration-Trade (30.0 mL)

Objective: To provide Astelin in a new package configuration that would be more patient friendly, require only one bottle per box/Rx, reduce cost of goods sold and comply with Phase IV commitment made to FDA to reduce particulates.

Background: The 30.0 mL V-bottom bottle/pump packaging configuration was approved via an SNDA. The placement of the pump during manufacturing was performed manually and resulted in particulate levels that conformed to release specifications of the current 17 mL configuration. The pump placing equipment at Decatur was never evaluated until September 2002 to determine if the mechanical installation of the pump would be able to result in acceptable particulate levels at release. The September 2002 feasibility study failed to achieve acceptable particulate levels. In addition, a considerable amount of operator intervention was necessary to remedy poor placement of the pumps into the bottle. A project team has been formed and an intense investigation of the entire process is being conducted. This investigation is focusing on the equipment and the two packaging components (bottle/pump). Historically the pump has been the major source of particulates and multiple attempts have been made in the past to reduce the amount of particulates.

Feasibility: Will be determined following engineering evaluation of bottle cleaning and pump placer equipment and all possibilities implemented to reduce the number of particulates associated with each packaging component.

Likelihood of Success: High. However, if the amount of particulates associated with the pump cannot be significantly reduced by the manufacturer and during the manufacturing process, a successful outcome does not seem likely.

Time: 6-9 months if the components for additional feasibility studies to be conducted in Jan/Feb are ordered now

Cost:Milestones/Go no Go Decisions:...

Configuration Approved	FDA approval	
Ordering Components	Oct/Nov 2002	\$170,000
Successful Feasibility Study	2-3 months	
Analysis of 3 PQ Batches (Stability)	9 months	\$170,000
Available for Launch	10 months	

Promotability: New package configuration will be fully promotable

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: V-Bottom Bottle-Sample (5 mL)

Objective: To provide Astelin in a new sample package configuration that would be more patient friendly, reduce cost of goods sold and comply with Phase IV commitment made to FDA to reduce particulates.

Background: The 5 mL V-bottom bottle sample was approved via an SNDA. The primary reason for this bottle was to allow use of the same spigot ring pump for both trade and sample and therefore reduce COGS.

Feasibility: Will be determined following engineering evaluation of bottle cleaning and pump placer equipment and all recommendations implemented to reduce the number of particulates associated with each packaging component associated with the trade product.

Likelihood of Success: Moderate to high. Engineering and particulate issues must be resolved with the trade product.

Time: 6-9 months following a successful feasibility study with the trade product.

Cost: Milestones/Go no Go Decisions:...

Configuration Approved	FDA approval
Successful Feasibility Study	TBD
Analysis of 3 PV Batches	TBD
Available for Launch	TBD

Promotability: NA

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Calmar-Albert Pump

Objective: To qualify a backup vendor for the supply of pumps in an effort to reduce COGS.

Background: Calmar-Albert has been working with operations to manufacture a pump that has comparable performance to the current Valois pump. After five years of work they have data to support further characterization of the pump (remaining tasks are outlined below) and may eventually be able to meet the current in vitro specifications.

Feasibility: Moderate.

Likelihood of Success: Moderate.

Time: 18-24 months

Cost: Milestones/Go no Go Decisions:...

Internal Resources (3 FTEs)	2 years	\$795,000
Feasibility (In vitro/pilot stability)	3 months	\$179,520
In Vitro Bioequivalence	6 months	\$486,000
Full Stability	12 months	\$950,000
Extractables	3 months	\$183,000
FDA Submission	3 months	
FDA Approval	6 months	

Promotability: None

Market Forecast:

FORMULATIONS PROJECTS

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Product: ASTELIN NASAL SPRAY

Project: Astelin/Steroid Combination

Objective: To develop a patent-protected combination of Astelin and a corticosteroid as a nasal spray.

Background: The technical aspects of developing this combination should be regarded as difficult. Issues that will need to be addressed include: (1) Astelin is a solution, virtually all nasal steroids are suspensions; (2) Astelin is administered twice daily, most steroids are administered once daily; (3) there may be compatibility issues between azelastine and steroids. In addition, full clinical development is required, and indications (SAR, VMR, Nasal polyps, etc.) must be studied individually. Dose ranges of each component must also be explored, and each component must contribute significantly to the overall effect, i.e., the FDA “combination rule”.

Feasibility: Low

Likelihood of Success: Low

Time: After formulation development, full dose-ranging studies and clinical trials will need to be conducted. Depending on the indications sought, it is expected that at least 4 to 5 years will be required prior to submission of an NDA, with approval approximately one year thereafter.

Cost: Total development costs would likely be \$75 to 100 million.

Milestones/Go no Go Decisions:...

<u>Milestone</u>	<u>Time</u>	<u>Cost</u>
Formulation Development	TBD	TBD
Clinical Development	TBD	TBD

Promotability: Advertising and promotion consistent with labeling.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Taste Masking-Meet Current Specifications

Objective: To generate a product that has reduced bitter taste objections by simple modifications of the formulation.

Background: The initial plan was to attempt minor modifications of the current formulation to mask the bitter taste and reduce objections. Numerous modifications were tried by PPD, however, all were either incompatible or resulted in significant changes to the in vitro specifications and will require extensive characterization and clinical studies. Hence, this short term fix is NOT feasible.

Feasibility: NONE-all modifications will alter specifications requiring extensive characterization of product, per the current regulatory guidance, new FDA submission and clinical trials.

Likelihood of Success: None

Time: N/A

Cost: Milestones/Go no Go Decisions:...

N/A

Promotability: N/A

Market Forecast: N/A

Product: ASTELIN NASAL SPRAY

Project: New Optimized Formulation

Objective: To improve dosing and reduce objections (primarily taste) by increasing API concentration, increasing viscosity, and possibly by the addition of sweeteners.

Background: Initial work indicated that any change to the current formulation results in what the guidance documents consider to be a major change and therefore require additional in vitro characterization, regulatory submissions and clinical trials for approval. Since any modification will follow this route to approval, the goal of this project is to create a formulation that is “optimal”. The drivers are: (1) decrease bitter taste (increase viscosity, add sweeteners, decrease dose (increase concentration of active)); (2) evaluate once per day dosing; and (3) create barriers to competition by issuing a new and improved formulation.

Feasibility: High. Technical aspects of formulation changes are achievable.

Likelihood of Success: Cannot be predicted. Requires a taste panel to determine if the formulation changes produce the desired effect.

Time: 3-4 years

Cost: Milestones/Go no Go Decisions:...

	Time	Cost
Internal Resources	3 FTEs (2 years)	\$795,000
Formulation Development	3-6 m	
Pump design/In Vitro Specs	18 m	\$1.2 M
GMP Manufacture	TBD	
Clinicals	TBD	
FDA Submission	TBD	

Promotability: Fully promotable, with the specific message dependent on the clinical data; however, this project would be successful if we could market a new and improved formulation with one spray per nostril BID dosing, and less bitter taste.

Market Forecast:

CLINICAL PROGRAMS

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Product: ASTELIN NASAL SPRAY

Project: One spray per nostril bid (Supplemental NDA)

Objective: Conduct two, double-blind, placebo-controlled, efficacy and safety studies in patients with SAR to support a change to the dosage and administration of the product labeling to indicate that the recommended dosage for adults 12 years of age and older is one or two sprays per nostril twice daily.

Background: Studies will be carried out by a CRO using investigators who are familiar with rhinitis protocols and/or who have participated in previous studies with azelastine nasal spray. Each study is three weeks in duration (1-week placebo run-in followed by a 2-week double-blind treatment period) and requires approximately 300 patients randomized to one of three treatment groups: (1) AzNS one spray/nostril bid, (2) AzNS two sprays/nostril bid, or (3) placebo nasal spray. Studies are conducted during the spring and fall allergy seasons using study designs that have been successfully implemented in previous company-sponsored investigations. Although no 2-week studies have been done in the U.S. with a one spray/nostril bid dosage regimen, this is the approved adult dosage in the EEC and there are several published double-blind, placebo- and comparative-controlled trials showing success with this dosage.

Feasibility: High. There are no foreseeable technical difficulties.

Likelihood of Success: Moderate

Time: Studies can be carried out over two successive allergy seasons (or could be conducted concurrently). Time from the beginning of protocol development to completion of a final study report is approximately 8 months for the first study. Lead-in time is approximately 3 months, which includes: (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval. The remaining 5 months involve the (1) conduct of the trial, (2) analysis of data, and (3) preparation of study reports. Assuming the first study is begun in March 2003 and has appositve outcome (final Clinical Study Report in July 2003), the Fall study can begin patient enrollment in late August/early September and be completed with a final report available during January 2004. Preparation of SNDA is 3 months with approximately 10 months for FDA review.

Cost: Each study requires approximately 300 patients for statistical analysis. The cost is estimated as follows:

Investigator Costs:	\$600,000.00 (\$2000 per patient x 300 patients)
CRO Cost:	\$375,000.00
Clinical Packaging:	\$ 50,000.00
EDC:	\$100,000.00
TOTAL COST:	\$1,125,000.00 per study

Milestones/Go no Go Decisions:

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate First Clinical Trial	March 2003	\$1.125 million
Completion of first double blind Trial	May 2003	
Final Clinical Study Report:	July 2003	
If data is positive perform 2 nd Trial:	September 2003	\$1.125 million
Completion of second DB Trial	November 2003	
Final Clinical Study Report	January 2004	
SNDA	March 2004	
FDA review	~January 2005	\$266,700.00

Promotability: Advertising and promotion, meetings and publications. The lower dosage option should reduce the incidence of taste problems associated with the two sprays per nostril bid regimen.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Perennial Allergic Rhinitis (Supplemental NDA)

Objective: Conduct two double-blind, placebo-controlled, efficacy and safety studies to obtain an indication for the treatment of PAR in patients 12 years of age and older at a dosage of two sprays per nostril bid.

Background: Studies will be carried out by a CRO using investigators who are familiar with rhinitis protocols and/or who have participated in previous studies with azelastine nasal spray. Each study is five weeks in duration (one week placebo run-in + four weeks of double-blind medication), and requires approximately 200 patients randomized to treatment with either: (1) AzNS two sprays/nostril bid or (2) placebo nasal spray. These studies would be based on protocols from our previous clinical programs in SAR and VMR. Our previous successes in SAR and VMR suggest that azelastine would be an effective treatment for PAR without the need for a pilot study. Also, European studies have demonstrated efficacy in PAR at a dosage of one spray per nostril bid.

Feasibility: High. There are no foreseeable technical difficulties in carrying out these studies.

Likelihood of Success: Moderate

Time: Studies can be carried out consecutively while avoiding the spring and fall allergy seasons. Time from the beginning of protocol development to completion of a final study report is approximately 8 months for the first study. Lead-in time is approximately 3 months, which includes: (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval. The remaining 5 months involve: (1) conduct of the trial, (2) analysis of data, and (3) preparation of study reports. Assuming that patient enrollment for the first study begins in February 2003 and the study has a successful outcome with a final report in June 2002, the second study can begin patient enrollment in November 2003 with a final report issued in March 2004. Preparation of SNDA is 3 to 6 months with approximately 10 months for FDA review.

Cost: Each study requires approximately 200 patients for statistical analysis. The cost estimated as follows:

Investigator Costs:	\$600,000.00 (\$3000.00 per patient x 200 patients)
CRO Costs:	\$450,000.00
Clinical Packaging:	\$50,000.00
EDC:	\$100,000.00

TOTAL COST: \$1,200,000.00 per study

Milestones/Go no Go Decisions:

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate First Clinical Trial	February 2003	\$1.2 million
Completion of first double blind Trial	April 2003	
Final Clinical Study Report:	June 2003	
If data is positive perform 2 nd Trial:	November 2003	\$1.2 million
Completion of second double-blind trial:	January 2004	
Final Clinical Study Report:	March 2004	
SNDA	June 2004	
FDA review	~April 2005	\$266,700.00

Promotability: Advertising and promotion, meetings and publications. Labeling change will expand the use of Astelin to include patients with both indoor and outdoor allergies. Astelin will be the only second-generation antihistamine with indications for SAR, PAR, and VMR.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Protocol 415 (Follow-on to Protocol 414 Claritin Failure Trial)

Objective: Conduct a double-blind, placebo-controlled, efficacy and safety study to evaluate the effect of Astelin Nasal Spray monotherapy, Clarinex monotherapy, and Astelin plus Claritin combination therapy versus placebo in patients with SAR who have had an unsatisfactory response to Claritin. This study is the follow-on to Protocol 414 and will be conducted according to an identical protocol.

Background: Assuming a positive outcome in P414, the study will be carried out by a CRO using investigators who participated in P414, or who have participated in previous studies with azelastine nasal spray and are familiar with rhinitis protocols. The study will be conducted during the Spring 2003 allergy season. This study is three weeks in duration beginning with a one-week baseline screening period, (during which patients are treated with open-label Claritin) which is followed by a 2-week double-blind treatment period. The study requires approximately 400 patients randomized to treatment with either: (1) AzNS two sprays/nostril bid, (2) Clarinex 5 mg qd, (3) AzNS two sprays/nostril bid plus Claritin 10 mg qd, or (4) placebo nasal spray. (It would be possible to use the same study design and substitute Allegra for Claritin as the lead-in drug or Allegra for Clarinex as an active treatment arm.)

Feasibility: High. There are no foreseeable technical difficulties in carrying out this study.

Likelihood of Success: Moderate.

Time: The study will be conducted during the Spring 2003 allergy season. Time from the beginning of protocol development to completion of a final study report is approximately 8 months. Lead-in time is approximately 3 months, which includes: (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval. The remaining 5 months involve the (1) conduct of the trial, (2) analysis of data, and (3) preparation of study reports. Assuming that patient enrollment begins in March 2003 and ends in May 2003, a final clinical report can be issued in July 2003.

Cost: The study requires approximately 400 patients for statistical analysis. The cost is estimated as follows:

Investigator Costs:	\$800,000.00 (\$2000 per patient x 400 patients)
CRO Costs:	\$650,000.00
Clinical Packaging:	\$250,000.00
EDC:	\$200,000.00

TOTAL COST: \$1,900,000.00

Milestones/Go no Go Decisions:...

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Positive outcome of P414	December 2002	
Initiate 2 nd double-blind trial	March 2003	\$1.9 Million
Final Clinical Study Report:	July 2003	

Promotability: Advertising and promotion, meetings and publications. The two studies can be used to position Astelin as (1) the treatment of choice for patients who respond poorly to oral antihistamines and (2) as an alternative to intranasal steroids in these patients.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: SAR and asthma

Objective: Conduct a double-blind, placebo-controlled, efficacy and safety study to determine the effect of Astelin Nasal Spray 2 sprays per nostril bid on seasonal allergic rhinitis symptoms and the impact of that effect on asthma symptoms in patients with both SAR and asthma. Allergic rhinitis and asthma often coexist in the same patient. Because of the relationship between the upper and lower airway, in patients with both rhinitis and asthma, controlling symptoms of rhinitis may also have a positive impact on asthma symptoms.

Background: Studies will be carried out by a CRO using investigators who are familiar with rhinitis protocols and/or who have participated in previous studies with azelastine nasal spray. The study can be conducted either during the Spring or the Fall allergy season using a protocol that was developed internally and reviewed by outside statistical and medical consultants. This study is three weeks in duration beginning with a one-week placebo lead-in period which is followed by a two-week double-blind treatment period. The study requires approximately 200 patients randomized to treatment with either: (1) AzNS two sprays/nostril bid or (2) placebo nasal spray.

Feasibility: High. There are no foreseeable technical difficulties in carrying out these studies.

Likelihood of Success: Low-to-moderate. A successful outcome depends on: (1) enrolling patients with a history of asthma exacerbations following exposure to seasonal allergens, (2) improving symptoms of SAR in these patients, and (3) the expectation that asthma symptoms will not worsen among patients treated with Astelin and will worsen among patients treated with placebo.

Time: The study can be conducted during the Spring or Fall allergy season. Time from the beginning of protocol development to completion of a final study report is approximately 11 months. Lead-in time is approximately 3 months, which includes: (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval. The remaining 8 months involve the (1) conduct of the trial, (2) analysis of data, and (3) preparation of study reports. Assuming that patient enrollment begins in March 2003 and ends in August 2003, a final report can be issued in October 2003.

Cost: The study requires approximately 200 patients for statistical analysis. The cost is estimated as follows:

Investigator Cost:	\$400,000.00 (\$2000 per patient x 200 patients)
CRO Cost:	\$450,000.00
Clinical Packaging:	\$50,000.00
EDC:	\$100,000.00

TOTAL COST: \$1,000,000.00

Milestones/Go No Go Decisions

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate Clinical Trial	March 2003	\$1.0 Million
Completion of DB Trial	August 2003	
Final Clinical Study Report	October 2003	

Promotability: Meetings and publications. Study is designed to position Astelin as the treatment of choice for SAR patients who also suffer from asthma. The study is consistent with positioning Astelin for specific types of rhinitis patients (85% of asthma patients also have allergic rhinitis).

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Somnolence/Cognitive Function Studies

Objective: Conduct two double-blind, placebo-controlled, sleep latency (Multiple Sleep Latency Test) and/or cognitive function studies (CogScreen or other test) to support a change to the clinical pharmacology section of the product labeling regarding effects in the MSLT and/or on cognition and psychomotor performance. The value of these changes must be assessed in the context of the AE section of the labeling remaining unchanged.

Background: Each individual study requires 60 patients randomized to active drug or placebo. Patients can undergo both MSLT and cognitive function testing within the same 2- to 5-day study period.

Feasibility: High. There are no foreseeable problems contracting the laboratories and sleep specialists to do this research.

Likelihood of Success: Moderate.

Time: Studies can be completed within a relatively short time frame at any time of the year. For both MSLT and cognitive function testing, subjects complete the evaluations in 2 to 5 days. Total time from beginning of enrollment to a final report is within 1 to 2 months. Lead-in time is approximately 3 months, which includes (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval.

Cost: Per patient costs are similar to those in clinical efficacy trials; however, fewer patients are required for statistical analysis. Total cost is estimated at:

Investigator Cost: \$210,000.00 (\$3500 per patient x 60 patients)

CRO Cost: N/A

Clinical Packaging: \$30,000.00

Data Management: \$30,000.00

TOTAL COST: \$270,000.00 per study

Milestones/Go no Go Decisions:...

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate First Clinical Trial	TBD	\$270,000.00
Completion of first double blind Trial:	1 month days from start	
Final Clinical Study Report:	2 months from start	
If data is compelling perform 2 nd Trial:	TBD	\$270,000.00
Completion of second DB trial:	1 month from start	
Final Clinical Study Report:	2 months from start	
SNDA	3 months to prepare	
FDA review	~10 months	\$266,700.00

Promotability: Advertising and promotion, meetings and publications. Labeling change could be used to support safety in pediatric patients and offset the labeled incidence of somnolence in SAR.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Nasal Polyps (Pilot Study)

Objective: Conduct an open-label, active-controlled, pilot study to evaluate the potential efficacy of Astelin Nasal Spray 2 sprays per nostril bid in the treatment of patients with nasal polyps.

Background: Studies will be carried out by a CRO using investigators who are familiar with studies in nasal polyposis. The study can be conducted any time of the year and consists of a 4-week washout period, during which no treatment for polyps can be used, followed by a 26-week open-label treatment period in which approximately 100 patients will receive either (1) Astelin Nasal Spray two sprays per nostril bid or (2) beclomethasone two sprays per nostril bid. Efficacy will be determined by patient assessments of symptom severity and investigator measurements of polyp size.

Feasibility: High. Other than the relatively long treatment period, there are no foreseeable technical difficulties in carrying out these studies.

Likelihood of Success: Low. The ability of Astelin to halt the progression of nasal polyps would appear to depend on anti-inflammatory effects of the drug. Although anti-inflammatory effects have been demonstrated in vitro and with oral formulations of azelastine, these effects have not been clearly established with the nasal spray formulation.

Time: The study can begin at any time during the year. Time from the beginning of protocol development to completion of a final study report is approximately 18 months. Lead-in time is approximately 3 months, which includes: (1) protocol and CRF development, (2) clinical packaging requirements, and (3) investigator recruitment, investigator documentation, and IRB approval. The remaining 15 months include 13 months to conduct the trial and 2 months for analysis of data and preparation of study reports.

Cost: The study requires approximately 100 patients for statistical analysis. The cost is estimated as follows:

Investigator Costs:	\$500,000.00 (\$5000 per patient x 100 patients)
CRO Costs:	\$250,000.00
Clinical Packaging:	\$50,000.00
EDC:	\$50,000.00

TOTAL COST: \$850,000.00 per study

Milestones/Go no Go Decisions:...

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate open-label pilot study	TBD	\$850,000.00
Completion of pilot study and Final Study Report:	15 months start of enrollment	
If data is positive perform double-blind trial:	TBD	\$850,000.00

Promotability: This pilot study is designed to assess the product's potential as a treatment for nasal polyps. If positive, the study could be published and presented at meetings. The study would also generate safety data related to the long-term use of Astelin Nasal Spray.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Pediatric Labeling (children 2 to 4 years of age)

Objective: Conduct a double-blind, parallel-group, placebo-controlled study to assess the safety and pharmacokinetics of azelastine and desmethy laz elastine in SAR patients 2 to 4 years of age.

Background: FDA required Wallace Laboratories to submit a Pediatric Study Request for patients in this age range; however, a recent Federal Court ruling determined that the Pediatric Rule (which is the basis for this request) exceeds the FDA's statutory authority and is invalid. This pediatric study, therefore, may not be required. If however the study is carried out, it will be contracted to a CRO using investigators who are familiar with pediatric rhinitis protocols. The study will be conducted during a sufficient number of allergy seasons to permit enrollment of approximately equal numbers of 2-, 3-, and 4- year-old patients. This study is two weeks in duration (2-week double-blind treatment period), and requires approximately 100 patients randomized to treatment with either Astelin Nasal Spray, one spray/nostril bid, or placebo nasal spray.

Feasibility: Moderate. Enrolling patients will be difficult and it may require two years to complete the analysis.

Likelihood of Success: Low to moderate. Data gathered under the study conditions dictated by this patient population may be difficult to interpret (uncertainties regarding effective administration of drug and the dosage delivered, second-hand reporting of adverse events, etc.).

Time: The study will be carried out during spring and fall allergy season with a final report to be submitted before July 1, 2005.

Cost: The study requires approximately 100 patients for statistical analysis. The cost is estimated as follows:

Investigator Costs:	\$250,000.00 (\$2500 per patient x 100 patients)
CRO Costs:	\$300,000.00
Clinical Packaging:	\$ 30,000.00
EDC:	\$ 50,000.00

TOTAL COST: \$630,000.00

Milestones/Go no Go Decisions:...

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate DB Trial	March 2003	\$630,000
Completion of DB Trial	August 2004	
Final Clinical Study Report	December 2004	

Promotability: Analysis of safety and pharmacokinetic data may be incorporated in appropriate sections of product labeling.

Market Forecast:

Product: ASTELIN NASAL SPRAY

Project: Non-allergic Asthma (NIH Study)

Objective: To evaluate the effect of Astelin in combination with intranasal steroids on signs and symptoms of non-allergic asthma. Also evaluated will be whether Astelin has any steroid-sparing properties.

Background: Oral formulations of azelastine have been studied in the treatment of allergic asthma and have demonstrated steroid-sparing effects in some patients. Dr. Jonathan Bernstein of the University of Cincinnati will conduct the research.

Feasibility: High. The study is being reviewed by NIH to determine if it will be funded. The study is completely feasible and we are being asked to provide active Astelin and matching placebo.

Likelihood of Success: Low to moderate.

Time: Once the study begins, it will take approximately six (6) months to enroll patients, followed by a one-year treatment period. Data will be available approximately two years following initiation of the trial.

Cost: No direct costs, drug supplies only.

Promotability: Publication.

Forecast: N/A

PRECLINICAL PROGRAM

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Product: Astelin (azelastine hydrochloride)

Project: Otitis Media (Animal Model)

Objective: Conduct a preclinical study in an allergic rat model with experimentally-induced otitis media to determine:

- If ototopically applied second generation H₁-antagonists have auditory toxicity and, if so, what is the therapeutic index (defined as dose to bring about auditory compromise divided by dose to bring about resolution of effusion) and
- If second generation H₁-antagonists improve clearance of middle ear effusion from allergic rats.

Feasibility: Study will be carried out at Vanderbilt University Medical Center by Drs. Labadie, Cutler, and Haynes in their otolaryngology laboratory. The study requires 50 animals randomized to one of the following experimental groups: (1) normal saline (control group), (2) diphenhydramine (8 mg/kg), (3) olopatadine, and (4) azelastine. The doses of olopatadine and azelastine are 100x and 1000x the recommended human dose.

This research may provide insight into the efficacy and safety of azelastine in the treatment of otitis media. Over 2 million outpatient visits occur per year due to otitis media. Approximately, 320,000 of these visits are estimated to be due in large part to the effects of allergy on the middle ear. Current therapy for ear infections does not include ototopically applied antihistamines which are commonly used in the nose and eye for allergy ailments.

Time: These animal studies will take approximately 2 to 3 months to complete. The investigator will supply the report of study results.

Cost: Cost of approximately 5 grams of azelastine hydrochloride and a several bottles of commercially available Astelin Nasal Spray.

Milestones/Go-No Go Decisions:...

<u>Milestone</u>	<u>Timing</u>	<u>Cost</u>
Initiate Preclinical Study	TBD	NA
Completion of Preclinical Study:	TBD	
Review of Final Report:	TBD	

Promotability: N/A. If safety and efficacy are shown in this animal model, could be used as springboard to human studies.

Market Forecast: N/A