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Seeking Insight

An Investor Update on Innovation

May 2010



Sun Pharma Advanced Research Company (SPARC Ltd.)
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BSE: 532872 • NSE: SPARC • BLOOMBERG: SPADV@IN • REUTERS: SPRC.BO

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SPARC – Innovating, with measured risk.



- A disciplined and systematic innovation process
- Focus on niche indications with predictable and sustainable market
- Develop products/technologies which solve unresolved problems and add meaningful value
- Early confirmation of the proof of concept
- Balanced resource allocation to projects of short and long gestation period
- Key approaches to research at SPARC
 - NDDS Approach
 - Improve patient compliance
 - Enhance safety
 - Reduced regulatory hurdles
 - Expand product indications.
 - NCE Approach
 - Work on validated targets and biology
 - Address limitations of current products
 - Improvement in therapeutic index and product PK characteristics

Technology Platforms



- ORAL

- Gastro Retentive Innovative Device (GRID)
- Wrap Matrix System

- INJECTABLES

- Nano particulate formulations
- Biodegradable Depot Injections.

- TOPICAL

- Dry Powder Inhalers (DPI)
- SMM Technology for Ophthalmic Formulations
- GFR Technology for Once a Day Ophthalmic formulations

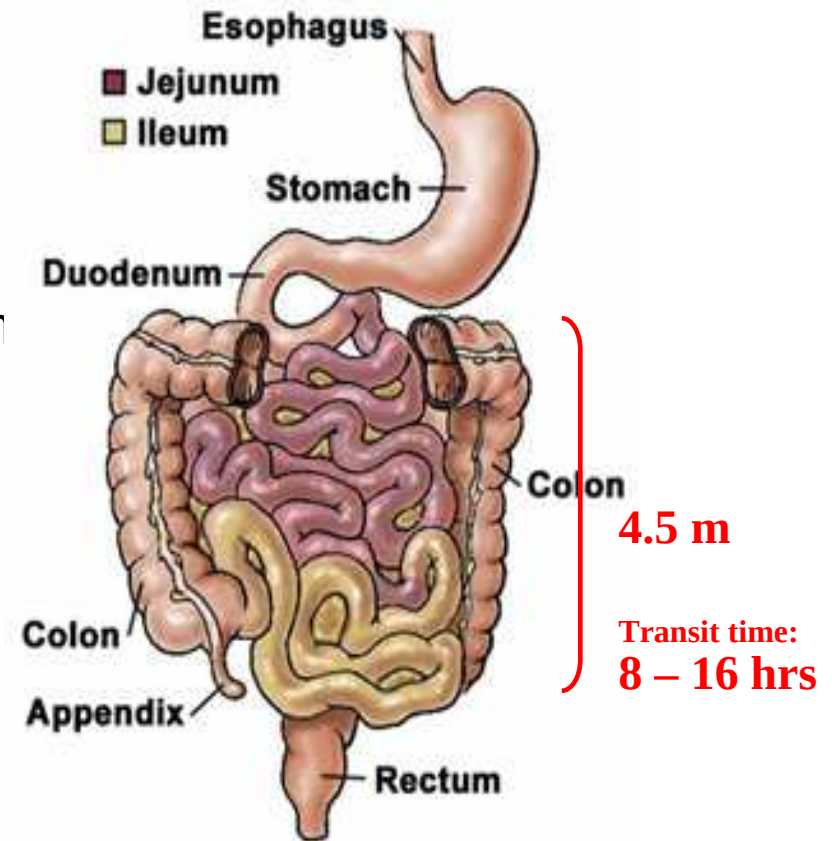


NDDS ORAL Products

Challenges in CR products with “Absorption Window”

• The Challenge

- Controlled release of drugs
 - Absorption from the small section of the upper GI tract
 - Transporter mediated absorption
 - Low solubility/degradation in intestinal fluid
 - Short and medium half-life
 - Transit of dosage form from the absorption area resulting into poor bioavailability



Gastro Retentive Innovative Device (GRID)



- **The Technology**

- Designed for retention in the stomach for longer time (~about 8 hours)
- Combination of mechanisms
 - Flotation
 - Size expansion
 - Mucoadhesion

- **Key Advantages of GRID Technology**

- Improves bioavailability of drugs with narrow zone of absorption in GI tract
- Floats instantaneously, Swells upto 8 times its initial volume
- Maintains physical integrity
- Flexible and soft
- Different types of release profiles possible (IR+ SR)
- Once – a day dosing improves patient compliance

Baclofen GRS Capsules



- Extended release capsule formulation of baclofen with Proprietary Gastro Retentive Innovative Device (GRID) technology
- Once daily and recommended fed state dosing for optimal bioavailability and minimal sedation
- Baclofen GRS capsules will be available in 6 strengths i.e., 10/20/30/40/50/60 mg for individualized dosing and greater dose flexibility

Baclofen GRS - Established Clinical Efficacy



- Total of 388 healthy volunteers and 108 patients exposed to baclofen GRS capsules
 - 19 studies for comparative bioavailability and observation of food effect
 - 11 pilot studies to optimize final formulation of baclofen GRS capsules
 - 8 studies to determine optimal dosing condition – q.d. with meal
- Summary of clinical studies in addition to PK evaluations
 - 4-Week Phase III clinical study in India in spastic patients
 - Successfully converted from Baclofen IR formulation to Baclofen GRS formulation
 - 2 Gastroscopy studies in spastic patients confirmed that there is no accumulation of capsules in stomach after multiple dosing

Baclofen GRS Future Development Plan



US

- 505(b)(2) route
- IND approved by USFDA
- Phase III, randomized, placebo controlled efficacy in 300 patients is initiated in USA
- One open label safety study in 100 patients and a PK study in patient population is planned

INDIA

- Baclofen GRS capsules are registered and marketed in India

Challenges in CR products with high solubility, high dose drugs



- High solubility and high dose challenges
 - Release control from dosage form
 - High excipient to drug ratio – bigger dosage form
 - Initial dose dumping
 - Difficult to achieve
 - Zero order release
 - Combination of release patterns like IR+SR, IR+SR+IR

Wrap Matrix System



- **The Technology**

- Novel oral controlled drug delivery system based on pre-defined, precise and selective surface exposure

- **Key Advantages of Technology**

- Once-a-day dosing
- Ability to handle products with larger daily dose
- Suitable for drugs with very high solubility
- No residual drug in dosage form on evacuation
- Minimal food effect
- Difficult to reproduce bioequivalence using any other formulation technology
 - Low risk of generics

Products with Wrap Matrix Technology



- An Antiepileptic with high water solubility and very large dose.
 - Phase II study in India ongoing
 - To be filed in US as 505(b)(2) in Q1 2011-12
- An Antihypertensive drug with high dose, high solubility
 - Phase II study ongoing
 - To be filed in US as 505(b)(2) in Q2 2011-12
- A Cardiovascular agent with high dose and high solubility
 - Pharmacokinetics studies are ongoing
- A skeletal muscle relaxant with ultra short half-life
 - Phase I studies ongoing
- CNS Agent with very high solubility
 - Pharmacokinetics studies are ongoing
- An Anticancer Agent
 - Pharmacokinetics studies are ongoing

NDDS – Injectable and Topical Products

The Challenge of Delivering Hydrophobic Anticancer Drugs



The Problem

- Water insoluble
- Non-selective bio-distribution – drug reaching in tumor as well as healthy organs

Conventional solution

- Use of toxic surfactants and non aqueous solvents

For e.g. _Cremophor® EL and Ethanol for paclitaxel and Polysorbate 80 and Ethanol for Docetaxel

- Surfactant based solvents do not solve this problem

Limitations

- Additional toxicity of surfactant limits the maximum tolerated dose
- Hypersensitivity of surfactant requires use of pre-medication
- Low tumor conc. of drug resulting into low efficacy, increased toxicity



Paclitaxel Injection Concentrate for Nanodispersion (PICN)

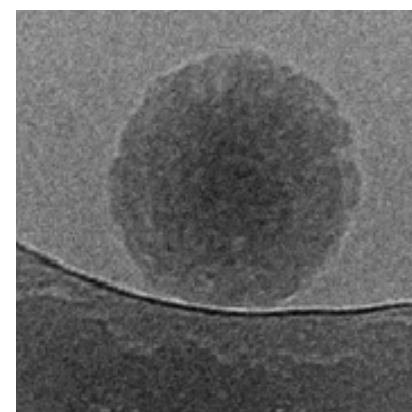
- Novel formulation of Paclitaxel using SPARC's proprietary nano particle platform technology
 - Achieves 30% higher drug concentrations in tumor tissues compared to conventional paclitaxel
 - Unlike ABRAXANE®, quick and easy “one step” dilution and infusion preparation
 - Shorter infusion time (30 min)
 - Superior safety profile compared to ABRAXANE®, observed in Phase I clinical study in INDIA.



PICN as How Supplied



PICN after Reconstitution



Electron microscope image of nano particle

Safety established at high doses in Phase I clinical trial



- Study enrolled 36 patients with metastatic breast cancer and who have progressed to at least one combination chemotherapy.

Lower dose limiting toxicities compare to ABRAXANE

KEY FINDINGS FROM INTERIM SAFETY DATA ANALYSIS

- 28 patients exposed with PICN.
- Dose limiting toxicity was observed at 325mg/m²
- NO pre-medication with high dose corticosteroids, antihistamines or anti-emetics.
- NO hypersensitivity reactions in ANY patients

	PICN 260mg/m ² n= 9 , (%)	ABRAXANE®* * 260mg/m ² n=229 (%)	TAXOL®** 175mg/m ² n=225 , (%)
Neutropenia <2.0 x 10 ⁹ /L <0.5 x 10 ⁹ /L	5(55.5) 1(11.11)	183(80) 21(9)	185(82) 50(22)
Neuropathy Any Symptoms Severe Symptoms	1(11.11) 0	163(71) 23 (10)	124(56) 7(2)

*This comparison with large historical data of Abraxane and Taxol is for the purpose of interpreting PICN data. PICN safety remains to be established in large, randomized clinical trial

** ABRAXANE PI

Encouraging trend of efficacy in Phase I clinical study



• KEY FINDINGS FROM INTERIM EFFICACY DATA ANALYSIS Trend of superior efficacy compared to ABRAXANE

- Efficacy of PICN is being evaluated for 2 dose levels.
 - 260mg/m² in 9 patients
 - 295mg/m² in 7 patients
- 3 patients achieved partial response, 3 with stable disease and 3 had disease progression in the 260mg/m² group with ORR of 33%.
- In the 295mg/m² group, 2 patients are dosed 5 cycles, 3 patients with 4 cycles and 2 patients with 2 cycles of treatment.
- No disease progression observed in ANY of these patients till date.

	PICN 260mg/m ² n= 9 , (%)	ABRAXANE ®** 260mg/m ² n=229, (%)	TAXOL®** 175mg/m ² n=225 , (%)
Objective response rate (ORR)	33%	21.5%	11.1%

*This comparison with large historical data of Abraxane and Taxol is for the purpose of interpreting PICN data. PICN efficacy remains to be established in large, randomized clinical trial

** ABRAXANE PI

Future development plan

- US –505(b2) route.
 - Pre-IND meeting with USFDA completed and obtained guidance from FDA for possible registration
 - To initiate Phase I study of a combination chemotherapy of PICN with Carboplatin Q3 2010-11
- India
 - To initiate a phase II/III study in metastatic breast cancer in Q2 2010-11



DICN Future development plan



- US –505(b2) route.
 - Pre-IND meeting with USFDA in FY 2010 – 11
- India
 - Initiated a phase I study in solid tumor patients

Challenges in Delivering Injectable Drugs for Chronic Use



- Chronic treatment of certain diseases require maintenance of systemic drug levels round the clock.
 - Products requiring daily injections for chronic treatment
 - Ultra short half life (Eliminated within minutes). e.g. Peptides
 - Poor patient compliance. e.g. Antipsychotic drugs
- There are long acting depot injections in the market which solve most of these problems. However, limitations are
 - Require high polymer to drug ratio
 - Use large size needle for delivery
 - Application requires training of the care givers
 - Require weeks to achieve desired therapeutic drug levels

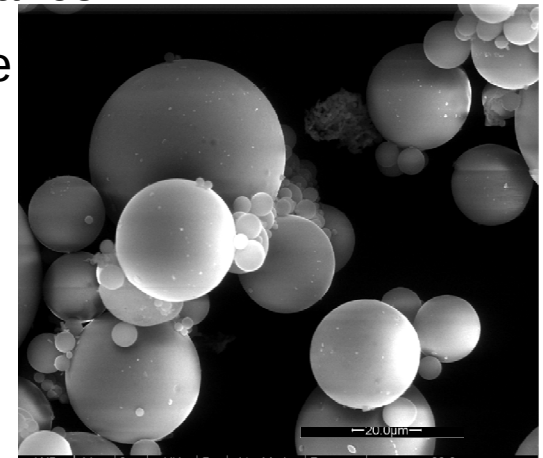
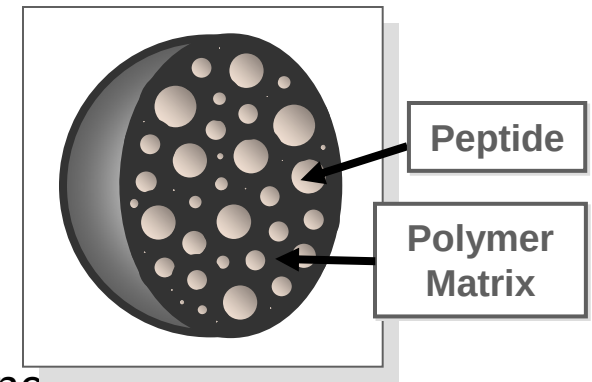
Biodegradable Depot Injections and Implants

• The Technology

- SPARC has developed a technology platform of biocompatible and biodegradable *micron-sized* polymer particles that contains drug molecule in its matrix for long-term systemic delivery of drugs.

• Key Advantages of Technology

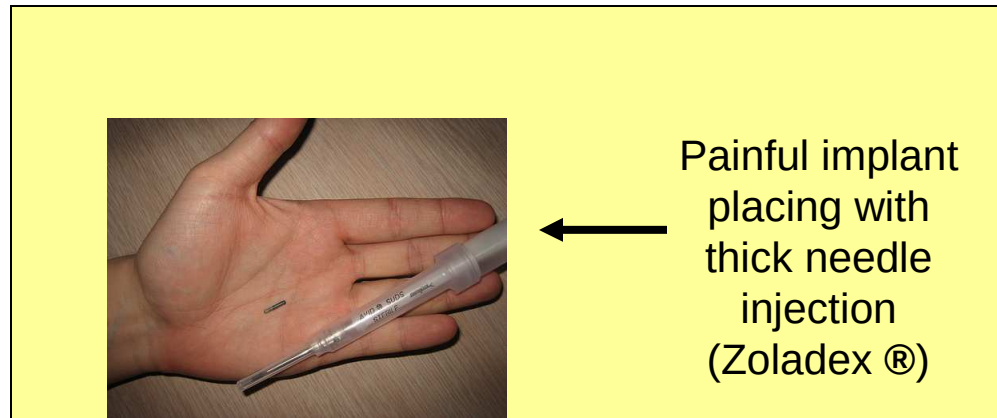
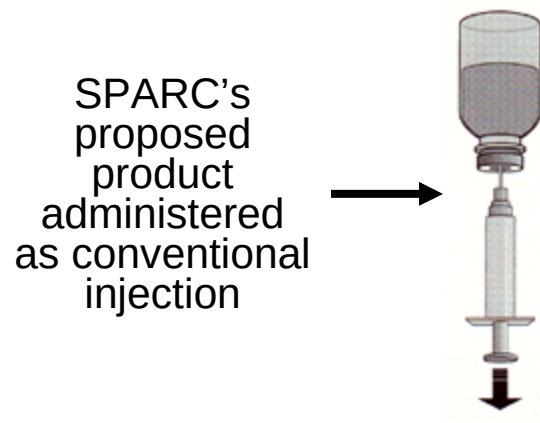
- Simple injections by IM/SC route; requires no specialized training for administration
- Fine needles, low injectable volume, better patient acceptance.
- Rapid onset and Prolonged release (for months in a single
- Uniform drug plasma concentration
- No peaks and valleys associated with daily and multiple doses - less toxic/adverse events
- Improves treatment adherence



Biodegradable Polymeric Microspheres

Goserelin Depot Inj. 1 Month

- Goserelin is a LHRH analogue used for the treatment of hormone dependant tumors such as prostate cancer, breast cancer & endometriosis.
- SPARC has developed Goserelin depot 1M Inj. using its proprietary biodegradable depot injection platform.
 - “Tailored release” to last drug in body for 1M single injection
 - “Tailored size” enabling use of “*thin*” (22 gauge) needles” for injection , unlike the innovator Zoladex® (Astra Zeneca) which uses “*thick*” (14 & 16 gauge) needles and considered “very painful”



Octreotide Depot Inj 1 M



- Octreotide depot Inj. (1 Month) is developed at SPARC with biodegradable depot injection platform.
- Chemical and Bioequivalence of this product with the Sandostatin® LAR has been established in series of studies undertaken at SPARC
- Octreotide depot Inj. is launched in India.

Future Development Plan



US

- Goserelin Depot Inj 1 M IND filing in Q1 2011 -12
- Octreotide Depot Inj IND filing in Q1 2011-12

INDIA

- Goserelin Depot 1 M Clinical trial is initiated in April'10

The Challenges of Delivering Inhaled Drugs

- Developing a Dry Powder Inhaler device that overcomes
 - Low drug delivery to lungs
 - Double dosing
 - Complex design and need for training of patient
 - Drug delivery dependent on inspiratory flow rate
- Developing a Dry Powder Inhaler which is compliant to the stringent US FDA and European requirements

Dry Powder Inhaler

The Technology

- SPARC's DPI is a pre-metered, 60 dose, inhalation activated device for administration of combination of inhaled steroids and bronchodilator drugs
- Uniform dose delivery independent of inspiratory flow rate
- Consistently delivers higher amount of drug to lungs
- Eliminates double dosing and dose wastage
- Provides visual, audible and tactile feedback upon dose administration
- Glow-in-the-dark feature for easy night-time use
- Feature for assisting visually impaired, as reminder to refill device, when 8 doses remain
- Small and convenient for easy to carry.
- Compliant to the stringent USFDA and European requirements.



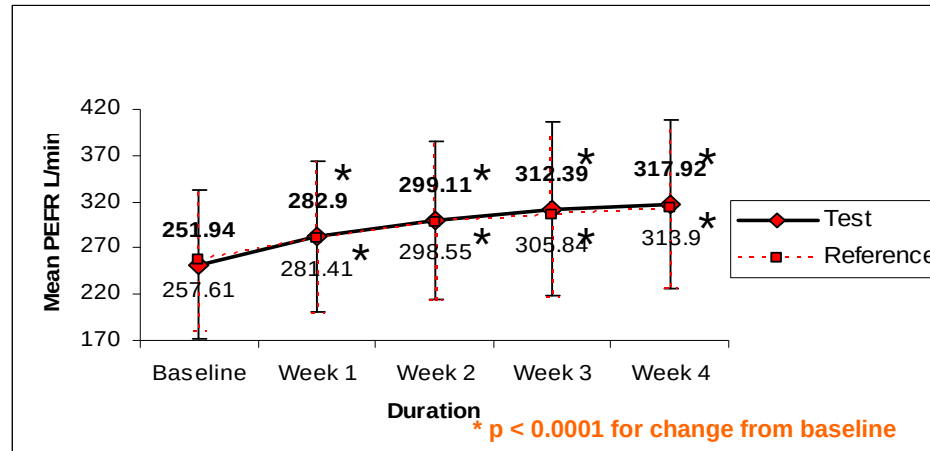
Equivalent clinical efficacy at half the dose of Seretide Accuhaler®



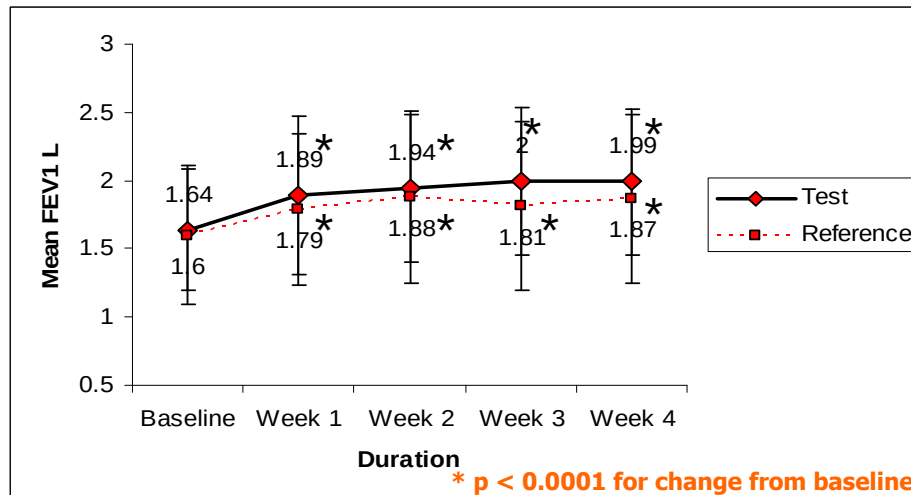
- Randomized, Comparative, Active Controlled, Multi-Center Study in Asthma Patients in India
 - Comparing
 - SPARC DPI containing Salmeterol **25mcg / Fluticasone 250mcg** (TEST) &
 - Seretide Accuhaler® –(Salmeterol 50mcg / Fluticasone 500mcg) (REFERENCE)
 - Treatment duration = 4 weeks, N = 113
- Study Outcome
 - **Equivalent efficacy** to Seretide Accuhaler® on all primary and secondary end points
 - SPARC's DPI demonstrated **statistically and clinically significant improvement vs. no treatment baseline in all efficacy parameters studied** (morning and evening PEFR and FEV1)
 - Efficacy of SPARC's DPI in improving lung function also demonstrated by reduction in use of rescue medication, by day and night time asthma symptoms, and by global impression of change rated by subjects and investigators

Equivalent efficacy at "half the dose" of Seretide Accuhaler®

Average Morning PEFR by Treatment Group by Treatment Week (n = 107)



FEV1 from baseline to week 4 (n = 107)



TEST = SPARC's DPI containing
Fluticasone 250mcg/Salmeterol 25mcg

REF = GSK's SERETIDE ACCUHALER®
Fluticasone 500mcg/Salmeterol 50mcg

Future Development Plan



- US – 505(b)2 route
 - Pre IND meeting in FY 2010-11
- India – Phase III study completed
 - To be launched in Q3 2010-11

Challenges in Ophthalmic Delivery of Lipophilic Drugs



Challenge

- Development of ophthalmic dosage forms of water insoluble prostaglandin analogues without the use of toxic surfactants.
- Stabilization of highly susceptible prostaglandins at ambient conditions

• Conventional solution

- Use of a preservative cum surfactant, benzalkonium chloride (BAK) at high conc. to solubilize the drug.
 - ❑ Requires storage at 2 – 8°C
- Chronic usage of BAK containing eye drops is harmful to the corneal surface. There is a regulatory concurrence in EU to replace BAK from ophthalmic solutions wherever possible.



Latanoprost “BAK Free” Ophthalmic Solution

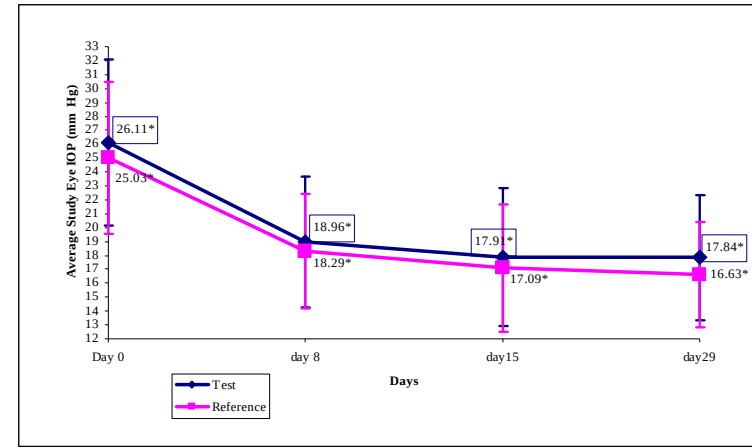


- Clear, colorless, BAK-free ophthalmic solution
- Non-infringing formulation to the market leader Xalatan® (Pfizer) with similar strength, dosing, administration and pack size.
- Reduced risk of ocular surface damage on chronic use
- Stable at Room Temp.; does not require refrigeration upon storage / transport
- Demonstrated improved safety profile and eye comfort characteristics in a phase III, randomized, active controlled clinical study in India in 100 patients.

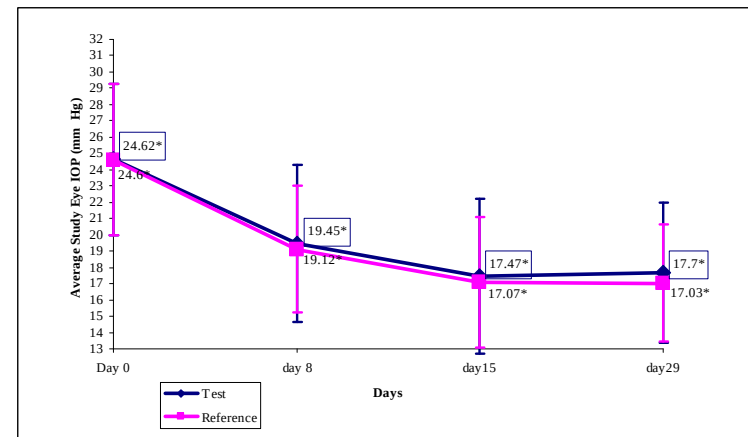
Equivalent Efficacy in Clinical Study in India

- SPARC completed a 4 week, randomized,, active controlled, multi-center, phase III study in India to compare safety and efficacy of SPARC's latanoprost with Xalatan®
 - 100 subjects were enrolled in this study
 - Clinically and statistically significant reductions in IOP was observed with SPARC's Latanoprost starting from 1 week and upto the 4 week study period.
 - Both efficacy and safety data were comparable to Xalatan®.

IOP (morning)



IOP (Evening)



Future Development Plan



- US – 505(b2) route
 - IND approved at USFDA
 - USFDA requires 2 Phase III studies for possible product registration
 1. An active controlled, non-inferiority, clinical study in 518 patients
 2. Open label extension safety study in 200 patients.
 - Target start date of the study: June 2010; Target study completion date; Q3 2012.
- India
 - Expected launch in Q2 2010-11

Challenges in Developing Once a Day Ophthalmic Formulations



The Challenge

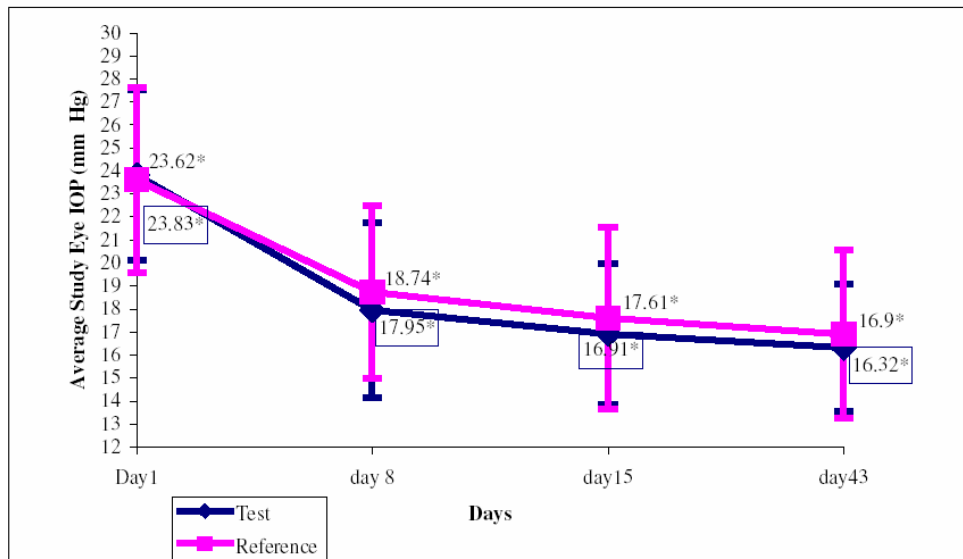
- To enhance the duration of action of short acting ophthalmic drugs
- Localization of drug action with minimal systemic absorption
- To make clear and non irritating formulation which does not cause
 - uncomfortable adhesion effects.
 - blurred vision upon instillation
 - burning and stinging.



Timolol Maleate Once a Day Ophthalmic Formulation

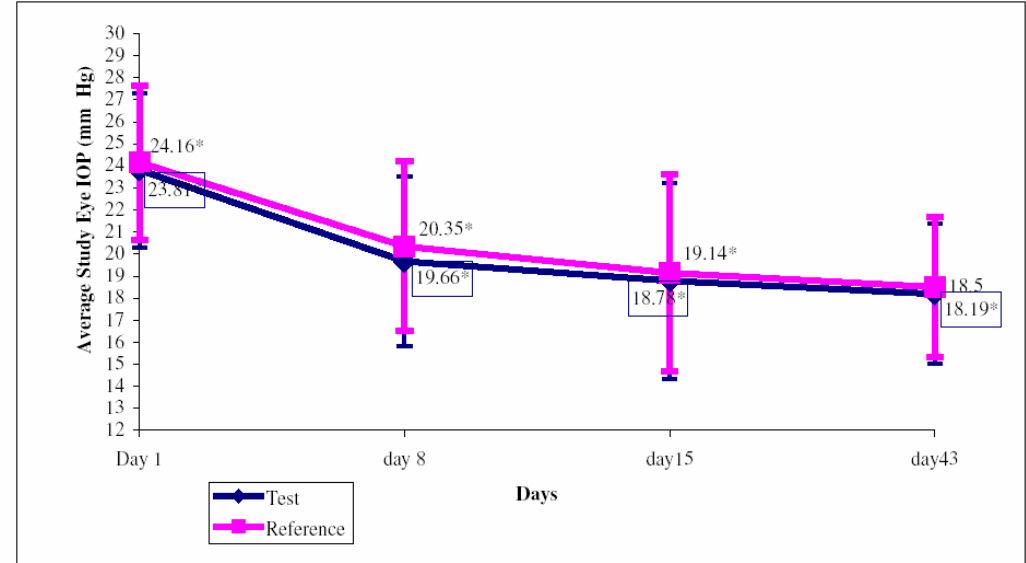
- Clear colorless solution
- Bioadhesive yet non-sticky.
- Lubricating-film forming and day time use possible
- Equivalent efficacy of Timolol maleate 0.5% administered once a daily was established in a clinical trial in 100 patients comparing with Timolol maleate 0.5% administered twice daily.

Average of Study Eye IOP (post-instillation) by Treatment Group - ITT Population



*p < 0.05 for change from baseline

Average of Study Eye IOP (pre-instillation) by Treatment Group - ITT Population



*p < 0.05 for change from baseline

Future Development Plan



- Phase III clinical study completed in India.
- Product launch in India – Q2 2010 - 12



NCEs

NCE candidates

- SUN-1334H
- SUN-597
- SUN-09
- SUN-44

Desired Attributes of a Novel Antihistamine

- Selective
- Non – sedating
- Quick onset and Long duration of action
- Cardiac safety
- Suitability for oral and topical route
- Anti-inflammatory potential

SUN-1334H Translating Preclinical to Clinical Advantage



- **Preclinical Studies**

- Highly selective histamine H1 receptor antagonist; insignificant affinity for other receptors
- Highly efficacious in allergic models
- High safety index
- Does not cross blood brain barrier as demonstrated in radio-labelled study
- Low potential for drug-drug interaction

- **Clinical Studies**

- Phase I completed in 127 healthy volunteers in India and Europe
 - Found safe up to 8 times the expected clinically efficacious dose
- 3 Phase II studies completed in total of 419 patients:
 - 1) SAR study in USA with 291 patients;
 - 2) CIU study in India with 131 patients;
 - 3) PAR study in India with 124 patients
- **Efficacy proof of concept established in Phase II studies**

SUN-1334H Ophthalmic Solution

- Although oral antihistamines can cause reduction in symptoms of conjunctivitis, the topical administration gives advantage of quicker onset and better efficacy
- In preclinical studies, SUN-1334H 0.3% ophthalmic solution, shows good inhibition of allergen and histamine-induced conjunctivitis upon once-a-daily dosing

Treatment	Edema Scores*	
	0.5 hr	24 hr
Saline	0	0
Placebo	17.67	16.42
SUN-1334H^a	3.75	3.42
Olopatadine^b	3.83	4.25

* Sensitized Guinea Pig Model; ^a 0.3% solution; ^b 0.2% solution

SUN 1334H Future Development Plan



- SUN 1334H Oral
 - Chronic toxicity studies are on going
 - Cardiac and renal safety studies and mass balance studies in human volunteers are planned
- SUN 1334H Ophthalmic
 - Completed Pre-IND meeting with USFDA
 - To begin Phase I clinical study in India – Q3 2010-11
 - IND filing in US after completion of Phase I study in India.

Desired Attributes of a Soft-steroid

- High efficacy on the target organs
- Long duration of action
- Suitable for different topical therapeutic application
- Low systemic bioavailability
- Rapid inactivation on systemic absorption
- Low potential for
 - Skin thinning
 - Increase in intra ocular pressure
- High therapeutic index

SUN-597 Superior Preclinical Profile



- ***In vitro***

- High binding affinity for human glucocorticoid receptor $K_i = 1.09\text{nM}$
- Good selectivity over other relevant sex hormone & mineralocorticoid receptors

- ***In vivo***

- Good potency, efficacy, and duration of effect in animal models of asthma and allergic rhinitis
- Low oral bioavailability and short half-life
- Very low liability to systemic side effects; thus providing a very high therapeutic index when compared with currently marketed corticosteroids

SUN-597 High Therapeutic Index in Asthma Model

SUN PHARMA
ADVANCED RESEARCH
COMPANY LTD.



Sephadex Lung Edema- ED₅₀ (Rat) (mg/kg, intratracheal)

Treatment	Lung Edema	Thymus Inhibition
SUN-597	0.094	> 3*
Ciclesonide	0.388	3.13
Fluticasone propionate	0.086	0.36

* 30% inhibition of thymus

Liver Glycogen Deposition (Rat) Dose: 3 mg/kg, 3 days, intratracheal

Treatment	Glycogen deposition (mg/100 gm liver wt.)
SUN-597	11.0
Ciclesonide	175.0
Fluticasone propionate	1955.8

Therapeutic Index (Lung Inflammation Model)

SUN-597	>32
Ciclesonide:	8.07
Fluticasone:	4.19

SUN-597 Low Side Effect Potential



Safety on Oral Administration in Rats

Dose: 1 mg/kg x 7 days

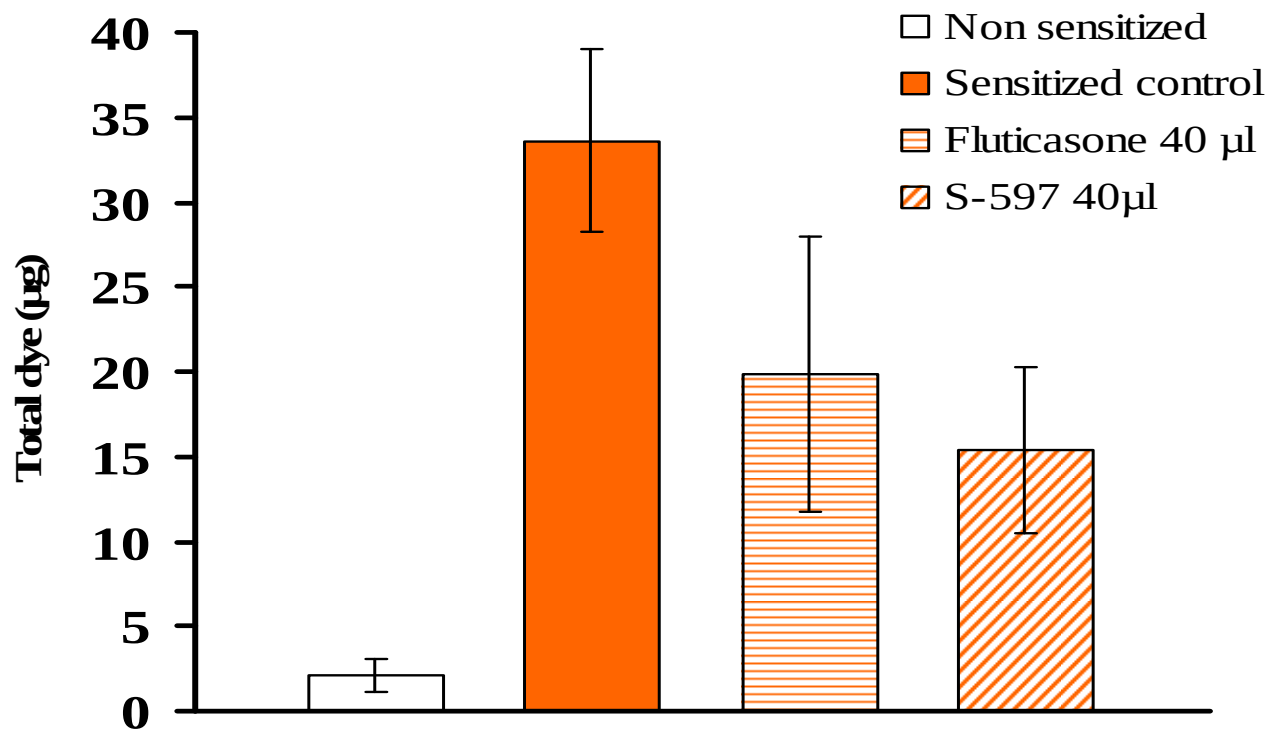
Treatment	% Inhibition of Thymus	% Inhibition of Adrenal	% Inhibition of Body Weight Gain
SUN-597	0	7.7	0
Ciclesonide	29.5	28.7	2.7
Fluticasone propionate	50.3	21.2	49.2

- No effect in 30-day intranasal tox study in rats (NOAEL: 2.5 mg/kg/day)
- No effect on serum cortisol levels in 30-day intranasal toxicity study in dogs

SUN-597 Nasal Efficacy in Allergic Rhinitis Model

SUN-597 as nasal formulation shows good potency and efficacy in preclinical *in vivo* models for allergic rhinitis

Nasal Formulation: 0.05% Suspension



SUN-597 Future Development Plan



SUN -597 Nasal

- Phase I clinical trials to commence in Q2 - 2010-11

SUN-597 Inhalation

- Dosage form development - FY 2010-11
- Sub-acute toxicity studies - FY 2010 -11

Desired Attributes of Pro-drugs of Drugs with Limited Absorption



- Avoid transporter absorption window
- Facilitated absorption throughout the GI tract
- Conversion of pro-drugs to active drug upon absorption
- Enhanced drug bioavailability
- Low toxic potential of pro-moiety
- Faster onset of action
- Dose dependent absorption
- Once a day dosage form
- Wider therapeutic application



SUN-09 Achieves Better Bioavailability of Baclofen



- In animal studies, intra-colonic administration of SUN-09 results in higher levels of baclofen compared to similar administration of baclofen
- Pharmacokinetic parameters viz. AUC is increased and T_{max} is reduced indicating higher and quicker absorption

Dose: 20 mg/kg, intracolonic in rat

Treatment	AUC _{0-t} (µg.hr/ml)	Tmax (hr)
Baclofen	1.17	2.4
Baclofen on SUN-09 administration	8.84	0.62

SUN-09 Significantly Superior Efficacy than Baclofen



- Oral administration of SUN-09 gives dose-dependent muscle relaxation with rapid onset of action in mice
- SUN-09 does not show additional safety concerns compared to baclofen in preclinical studies

Percentage Reduction of Rotarod Performance in Mice

Treatment	Dose (mg/kg, p.o.)	% Reduction
SUN-09	20.8	53.6
	31.2	81.2
	52.0	97.5
Baclofen	12.0	44.7
	18.0	47.0
	32.0	48.2

On a molar basis, doses of SUN-09 are equivalent to respective doses of baclofen

SUN-09 Future Development Plan



INDIA

- IND approved by DCGI
- Phase I clinical study to commence in Q3 2010-11

SUN-44 Promising Preclinical Profile

- SUN-44 is a pro-drug of gabapentin intended to increase bioavailability (drug exposure), hasten onset of effect and reduce inter-individual variability
- Limitations in the pharmacokinetic properties of gabapentin provide scope for improvement
- SUN-44 gets rapidly absorbed and converts to gabapentin in experimental animals
- Pharmacokinetic profile in rats indicates higher AUC and lower T_{max} for gabapentin release by SUN-44 at equivalent doses of gabapentin

Treatment	Dose (mg/kg, p.o.)	AUC _{0-t} (µg.hr/ml)	Tmax (hr)
Gabapentin from gabapentin	100	88.14	2
	2000	682.74	4
Gabapentin from SUN-44	200	177.43	1
	4000	2187.06	1

On a molar basis, 200 and 4000 dose of SUN- 44 are approximately equivalent to 100 and 2000 mg/kg doses of gabapentin, respectively

SUN-44 Superior to Gabapentin

- In animal model of epilepsy, SUN-44 shows better efficacy compared to gabapentin
- SUN-44 reduces the latency and incidence of tonic extensor and increases the protection from mortality

Treatment	Dose (mg/kg, p.o.) (Mice)	% Incidence of Tonic Extensor	% Protection from Mortality
SUN-44	35	37.5	40
	70	0.0	100
Gabapentin	35	75	0
	70	37.5	40

- Preclinical safety studies do not indicate additional liabilities in terms of safety
- SUN-44 as a pro-drug does not release reactive acetaldehyde moiety, hence no alteration of protein or enzymes are expected. Neither there is possibility of acetaldehyde related organ toxicities such as liver, brain and cardiac toxicity, or hypersensitivity reactions. Thus, no additional safety concerns are anticipated

SUN-44 Future Development Plan



- IND filed in INDIA
- Phase I to commence in FY 2010 - 11

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Thank you

For updates and specific queries, please visit www.sunpharma.in
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