sirnaomics
Advancing RNAi Therapeutics

Sirnaomics Ltd. (2257.HK)

STP705 isSCC Clinical Phase Update

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Presenters

Patrick Lu, PhD

Founder, Chairman of the Board,
Executive Director,

President & CEO

28+ years of experience

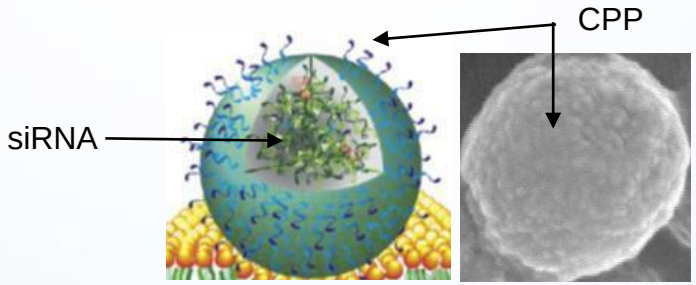
Kevin Li, MD

VP of Medical Affairs

26 years of experience

Two Proprietary Delivery Platforms and Therapeutic Areas

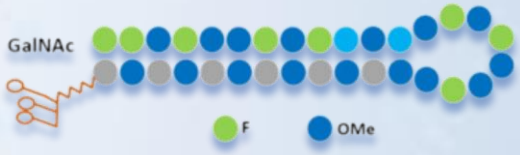
1 **PNP Platform**
(Clinical Stage)



HKP and HKP(+H) are well suited for siRNA Therapeutics
or mRNA Therapeutics and Vaccine Deliveries

2 **GalNAc Platform**
(Clinical Candidate)

GalAhead®

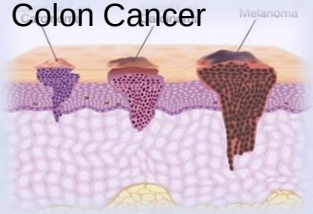


mRNA

Vaccine
Neoantigen Vaccine
Protein Replacement
mRNA Antibody

Cancer

NMSC (isSCC, BCC)
Liver Cancer
Lung Cancer
Pancreatic Cancer
Colon Cancer



Fibrosis Diseases

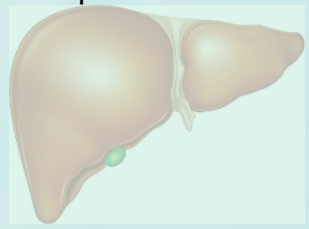
Skin Scar, Keloid
Liver Fibrosis
Lung Fibrosis
Kidney Fibrosis

Viral Infections

Influenza
SARS-CoV2
HBV
HPV

Liver Metabolic Diseases

Anti-Coagulant
LDL Deregulation
High Blood Pressure
Compliment Disease



Prioritized Product Pipeline Advancing Oncology Programs

	Candidate	Gene Targets	Indications	Delivery Platform	Pre-clinical	IND Enabling	IND	Phase I	Phase II	Phase III	Rights	Status
Oncology	STP705	TGF-β1/COX-2	isSCC	PNP-IT							Global	Communicating with FDA re late-stage trial
			BCC								Global	Data readout in Q2 2023, Communicating with FDA re late-stage trial
	STP707	TGF-β1/COX-2	Multiple solid tumors	PNP-IV							Global	Interim data readout completed in Q4 2022
Medical Aesthetics	STP705	TGF-β1/COX-2	Fat remodeling	PNP-subcutaneous							Global	Data readout in Q2 2023
Antiviral	STP702	M1/PA	Influenza	Airway / PNP-IV							OL China	Continue partnership
	RV-1730[1]	SARS-CoV-2	Covid-19 vaccine	LNP Intramuscular							Global	IND approved by FDA
GalAhead™	STP122G	Factor XI	Anticoagulation / Thrombosis	GalAhead™ subcutaneous							Global	First Patient In
	STP125G	ApoC3	Hypertriglyceridemia								Global	IND in 2023
	STP144G	Complement Factor B	Complement-mediated diseases								Global	IND in 2024
	Seven Other Early-Stage Assets										Global	

Abbreviations:
isSCC= cutaneous squamous cell carcinoma in situ; BCC= basal cell carcinoma; PNP = our polypeptide nanoparticle (PNP) RNAi delivery platform; PNP-IT = PNP platform formulated for intratumoral administration; PNP-IV = PNP platform formulated for intravenous administration; PNP-ID = PNP platform formulated for intradermal administration, GalAhead = our GalNAc RNAi delivery platform that conjugates GalNAc moieties to RNAi triggers; LNP = lipid nanoparticle (LNP) formulation for delivery of mRNA; OL China = out-licensed mainland China, Hong Kong, Macau, and Taiwan rights under agreement with Walvax but we retain the rights for rest of the world.

Note:
1. Research and development conducted by our subsidiary RNAimmune.

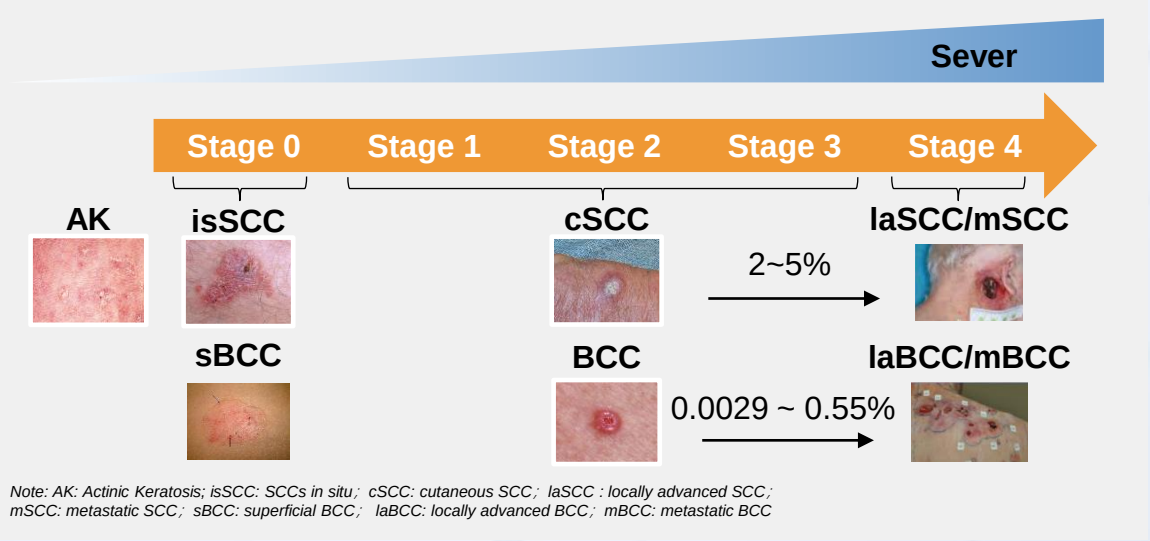
Priority to advance STP705 to late-stage development and validation of PNP platform with positive STP707 data. Dual platform play increases possibility of success of drug development

Non-Melanoma Skin Cancers（NMSC）

One of the most common cancers in the U.S. with growing market potential

Overview

- BCC and SCC account for the majority of NMSCs with more than five million newly diagnosed cases estimated to occur in the U.S. every year
- Squamous cell carcinoma in situ (isSCC), also known as Bowen disease, is the earliest form of squamous cell carcinoma



Note: AK: Actinic Keratosis; isSCC: SCCs in situ; cSCC: cutaneous SCC; laSCC : locally advanced SCC; mSCC: metastatic SCC; sBCC: superficial BCC; laBCC: locally advanced BCC; mBCC: metastatic BCC

Market Drivers

- Exposure to **UV radiation**
- The **incidence of precancerous skin conditions** such as actinic keratoses, moles and freckles, owing to an **aging population**
- **Genetic susceptibility to diseases**
- **More treatment options** available
- Country-wide skin cancer screening was introduced and became more prevalent for residents older than 35 years of age with health insurance since 2008 in the U.S., leading to an **increase in diagnosis rate**

Source: Prospectus Industry Report, CIC, Boston Consultant Group
Note: （1）sum of the U.S. and China.

Annual number of deaths from SCC or BCC in the U.S.
> 18,000

57% Head / Neck

42% Trunk / extremity

BCC and SCC prevalence from 2015 to 2020
+33%

Number of cases of SCC [1]

3.2m	Estimate 6.8m
2020	2030

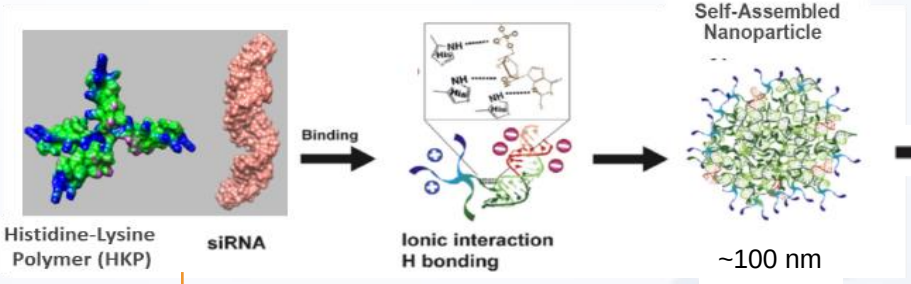
Number of cases of BCC[1]

2.5m	Estimate 4.4m
2020	2030

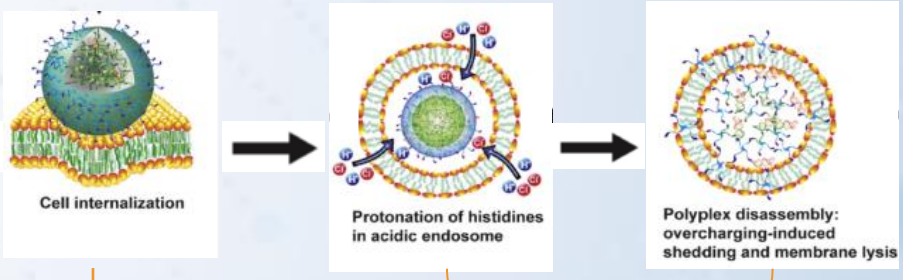
Unmet needs: further improvements in skin appearance and convenience is the key

Unique Property of PNP (HKP) for siRNA Delivery

Structure



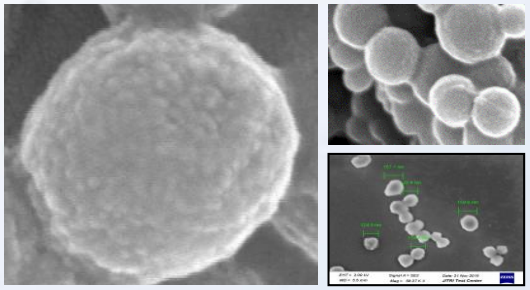
Mechanism of delivery



Inherently safe structure

- **Biodegradable** histidine-lysine branched polypeptides
- **Polypeptides with no chemical modification required**, **Low immunogenicity in preclinical and clinical studies**
- **Stable in human body in absence of chemical modification**
- Gene knockdown activity:
  - 7+ days in the skin
  - Up to 4 days in tumors
  - 16 days in the tissues around the eyes and the eyeball (injection)
- **Large scale manufacturing with microfluidic technology**

Unique properties for PNP



- **PNP** has a rough surface, with **cell penetration property (“CPP”)**
- Possible to envelop and protect **10k-100k siRNA** into HKP to facilitate delivery into the targeted tissue & cell
- Controlled release property
- Can enter target activated endothelial cells through the **NRP1** receptor

Efficient endosome escape

- The percentage of endosome escape translates to the efficiency of delivery of siRNA. PNP-siRNA has shown high endosome escape efficiency

Prof. Jim Mixson
University of Maryland
Inventor of HKP

Sirnaomics have PNP exclusive global patent rights on PNP

Polypeptide Nanoparticle Platform for RNA Delivery

Backbone PNP delivery platform is a potential game changer

Significant advantages against existing platforms

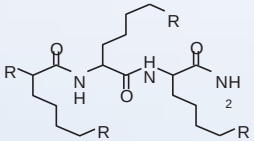
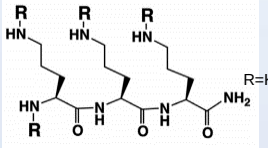
High delivery efficiency
for both local and systemic applications

Validated safety
tested locally in human and systemically in NHP

High packaging efficiency
>97% loading, can carry multiple RNA molecules

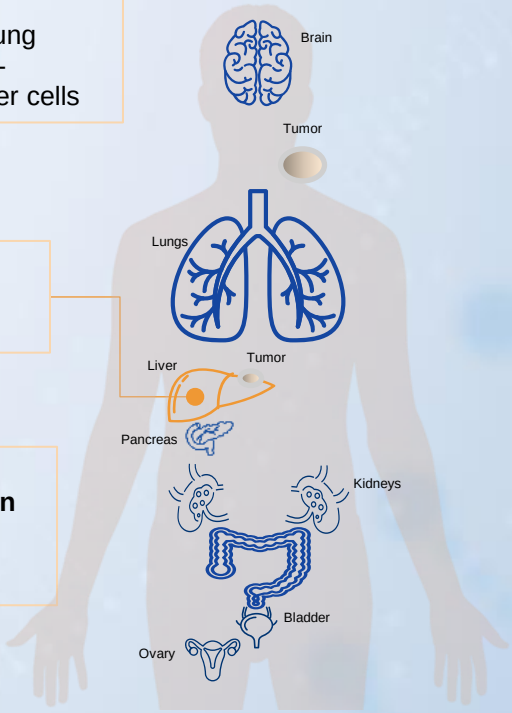
Simple and stable Formulation
easy synthesis process, no cold chain storage required

Highly efficient for broad applications using different encapsulating peptides

HK Peptides		Applications	siRNA	mRNA
KHHHKHHHKHHHKHHHK	=	H3K	√	
 R=KHHHKHHHKHHHKHHHK	=	H3K4b, brunched	√ (local)	
 R=KHHHKHHHKHHHKHHHK	=	H3K(H)4b, branched	√ (systemic)	√

siRNA is much more than for hepatocytes of the liver

- ✓ **A wide range of organs targeted:** Tumor cells, lung cells, and non-hepatocyte liver cells
- ✓ **Multiple** liver cell types targeted
- ✓ **Multiple administration routes:** IV, IT



*The organs shown in the picture are targeted

- **Current Clinical Uses:** isSCC (Ph IIb), BCC (Ph II), Keloid (Ph 1/2), HTS (Ph IIa), liver cancer(basket) (Ph 1), Solid tumors (Ph I)
- **Planned Clinical Uses:** Solid tumors, liver cancer, Cholangiocarcinoma, pancreatic cancer, Colorectal Cancer, NSCLC, cSCC, lung fibrosis, liver fibrosis, etc.

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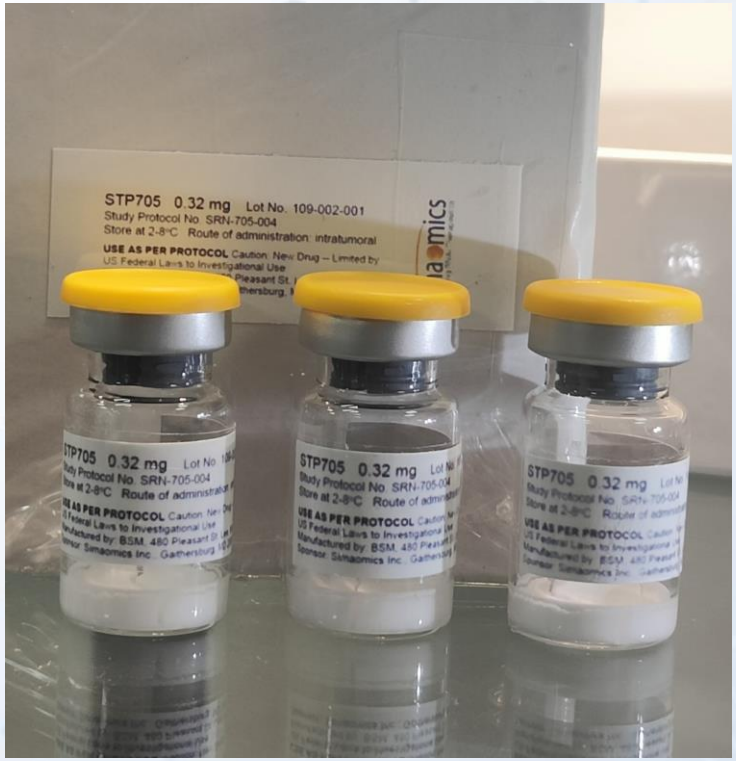
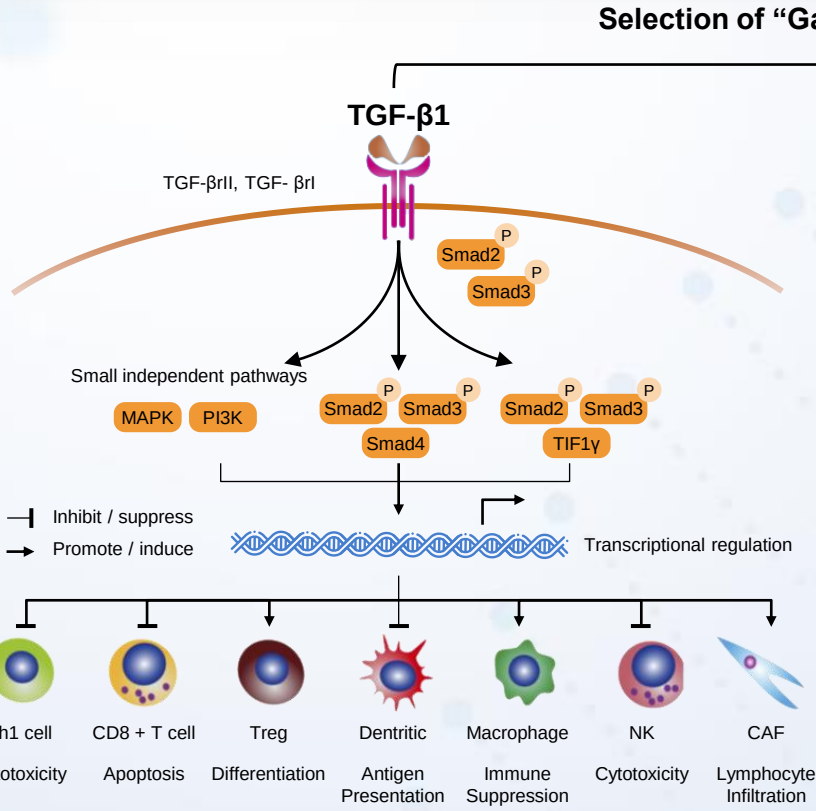


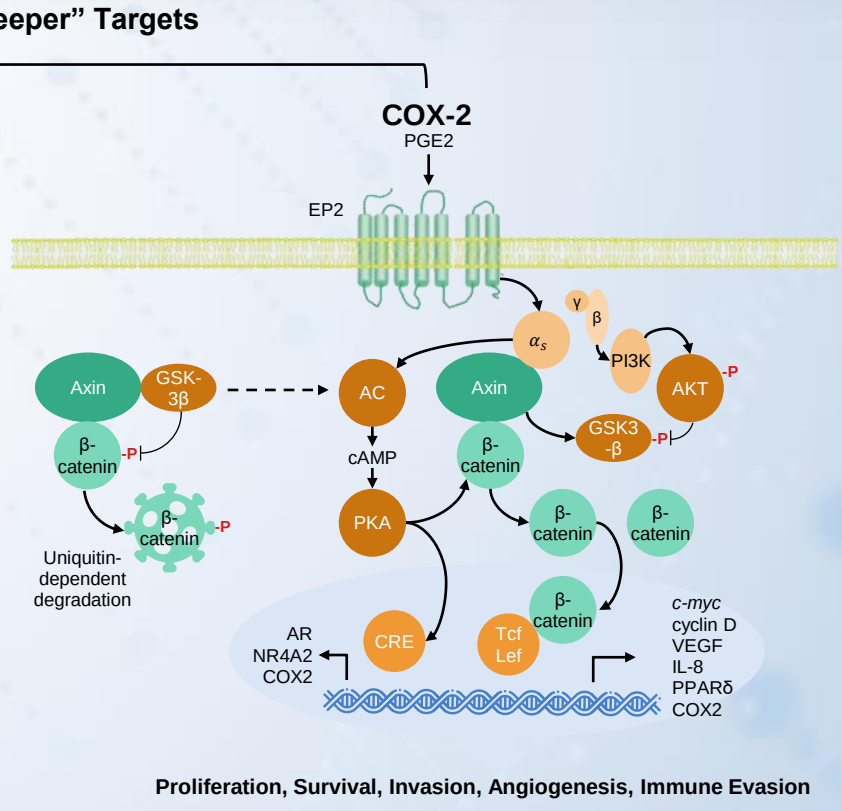
Core Product STP705 (Local Formulation)

Innovative Dual-Targeted RNAi Therapeutics

Targeting both TGF-ß1 and COX-2



Source: *Bai, X., et al. OncoTargets and Therapy, 2019: 12, 9527–9538.*



Source: *Hashemi Goradel N, et al. J Cell Physiol. 2019: 234, 5683-5699.*

Mechanism of Action: The mechanism of action for both **TGF-β1** and **COX-2** in tumor biology and fibrotic disease is widely recognized

Drugability: A dual-targeted RNAi drug design inhibits both **TGF-β1** and **COX-2** simultaneously for high therapeutic potency

Minimize Toxicity: PNP delivery platform enables to create cell- and tissue-selective targeting of the TGF ß1/COX 2 inhibitory activity provided by the siRNA therapeutic and **avoiding whole body exposure**

Drug Formulations: Local formulation **STP705** uses **HKP**, and systemic formulation **STP707** uses **HKP+H**

Key Publication: Simultaneous silencing of TGF-β1 and COX-2 reduces human skin hypertrophic scar through activation of fibroblast apoptosis, *Lu, Li et al.* **Oncotarget**, 2017 (9)

IP Protection for this Key Asset: Strong intellectual property position

Preclinical - Confirm Effective Dosage & Interval

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 46), pp: 80651-80665

Research Paper

Simultaneous silencing of TGF-β1 and COX-2 reduces human skin hypertrophic scar through activation of fibroblast apoptosis

Jia Zhou[1,*], Yixuan Zhao[1,*], Vera Simonenko[2,*], John J. Xu[3], Kai Liu[1], Deling Wang[3], Jingli Shi[3], Tianyi Zhong[3], Lixia Zhang[3], Lun Zeng[4], Bin Huang[4], Shenggao Tang[5], Alan Y. Lu[5], A. James Mixson[6], Yangbai Sun[1], Patrick Y. Lu[2] and Qingfeng Li[1]

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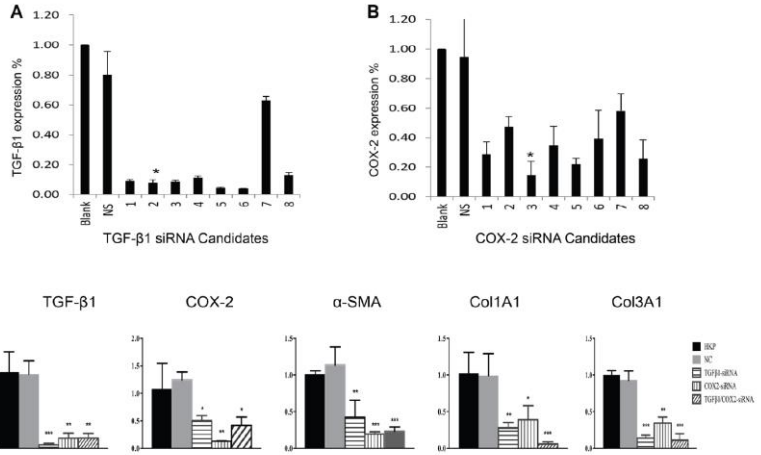
Keywords: *siRNA therapeutics, hypertrophic scar, TGF-β1, COX-2, synergistic effect*

Received: *November 16, 2016* ***Accepted:*** *August 26, 2017* ***Published:*** *September 14, 2017*

HKP enhances siRNA delivery into human hypertrophic scar

To ensure efficient siRNA delivery to the hypertrophic scar, we selected a biodegradable histidine-lysine polypeptides (HKP) that has been demonstrated to provide efficient siRNA delivery *in vivo* [17, 18]. When HKP and siRNA are mixed in aqueous solution with an optimized N/P ratio (4/1; weight/weight), self-assembly of nanoparticles occurs through electrostatic and non-ionic bonds. These nanoparticles can be lyophilized into dry powder and then re-formulated with aqueous solution (Figure 3A, Supplementary Figure 4). The lyophilized HKP (TGF-β1/COX-2siRNA) nanoplex powder once re-



HKP-packaged TGF-β1/COX-2 siRNA (STP705) reduces size of human hypertrophic scar

As expected, we found that TGF-β1 and COX-2 were significantly over-expressed in human hypertrophic scar (HS) tissue from patients compared to normal skin tissue (Figure 4A). Human HS tissues were implanted onto nude mice subcutaneously for studying the pathophysiology of HS and the efficacy of siRNA silencing. After HS tissue was implanted, we analyzed these tissues at day 7, day 14 and day 28 post implantation. We then isolated mRNA from the tissue samples to determine the expression dynamics of TGF-β1, COX-2 and α-SMA using qRT-PCR analyses (Figure 4B). The expression of TGF-β1 and COX-2 in the implanted human scar tissues exhibited an unexpected pattern with a rapid increase of TGF-β1 versus a steady increase in COX-2. The TGF-β1 expression reached a peak level at day 14 while COX-2 expression was still up regulated on day 28 post implantation.

Based on the results from Figure 3D and Figure 4B, we initiated treatment on the implanted human hypertrophic scars on mice four weeks after surgery. A 20 μg/50 μl /cm3 HKP (TGF-β1/COX-2siRNAs) was administered to each scar implant using 5 aliquots into 5 different sites of the scar, with three repeated injections at 5 days intervals. The STP705 combination treated HS implants showed a significant reduction in size of implanted tissues at day 28 post-treatment (Figure 4C–4D), by about 45% compared to the untreated group. After tissue samples from those implants were further analyzed, we found that not only the targeted genes TGF-β1 and COX-2 were significantly silenced based on the qRT-PCR results, but other proteins such as α-SMA and col1A1 were also

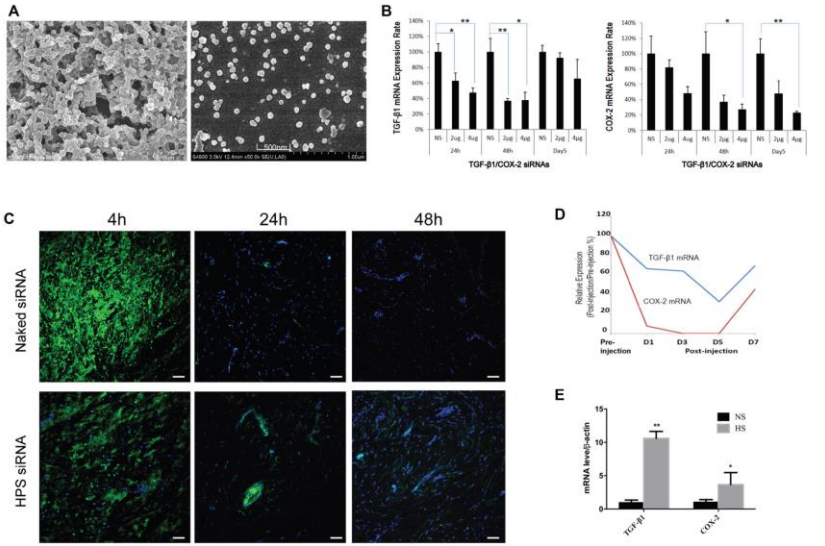


Figure 3: HKP Enhances Intra-scar Delivery of siRNA (**A**) SEM image of HKP (TGF-β1/COX-2siRNAs) nanoparticles. After resuspension of lyophilized HKP (siRNA) nanoparticles in aqueous solution, these particles had an average size of 150 nm in size and similar size distribution, properties of which are typical for intra-scar siRNA administration. (**B**) Real-Time qPCR analysis of the tissue samples revealed HKP packaged TGF-β1/COX-2siRNAs knocking down TGF-β1 and COX-2 in a dose-dependent manner. Whereas TGF-β1 was down regulated more between 24–48 hours post treatment, COX-2 decreased more between 48 and 96 hours post treatment ($n = 6$). NS is Lu25-a 5′-r(GAGGAGCCUUCAGGAUUACAAGAUU)-3′ 5′-r(AAUCUUGUAAUCCUGAAGGCUCCUC)-3′, at 2μg serving as control siRNA. (**C**) The siRNA-Alexa Fluor labeled and HKP-packaged siRNA-Alexa Fluor labeled were compared *in vivo* for their duration and dispersion after local intra-scar injection, using human hypertrophic scar tissue implant model with mice, at three time points: 0 hour, 24 hour and 48 hour post administration. HKP formulated siRNA resulted in a prolonged siRNA duration after intrascar injection into human hypertrophic scar implant. (**D**) Injections of HKP (TGF-β1/COX-2siRNAS) nanoparticle solution into the human hypertrophic scar resulted in down regulations of TGF-β1 and COX-2 expressions in the tissue, up to 5 days, based on the qRT-PCR analyses. (**E**) Comparison of TGF-β1 and COX-2 expressions in human normal skin tissue (NS) and human hypertrophic scar tissue (HS) ($n = 3$, $^*P < 0.05$).

STP705 - Provides Positive Clinical IIa Results for isSCC

Ph IIa Study design and results

Professor Brian Berman, MD/PhD, Univ. Miami

- A total of up to **25 subjects** with diagonized isSCC, 5 cohorts
- Intratumor injection with 5 different dosage groups
- Giving the right dosage to each subject for once a week for up to **6 weeks.** Histology Analysis at week 7 for completed clearance (primary endpoint)

40% (2/5)	60% (3/5)	80% (4/5)	100% (5/5)	80% (4/5)
10μg	**20μg**	**30μg**	**60μg**	**120μg**

Result 1: 19/25 reach to the primary endpoint (76%)

Result 2: 30μg and 60μg groups demonstrated the best results (9/10) with 90% efficacy

Result 3: No SAEs, no TEAEs related to the study

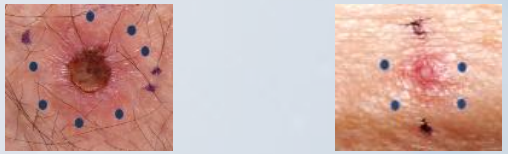
Result 4: Improved cosmetic appearance

Selection of effective and safe dosage 30μg and 60μg for Clinical Phase IIb study

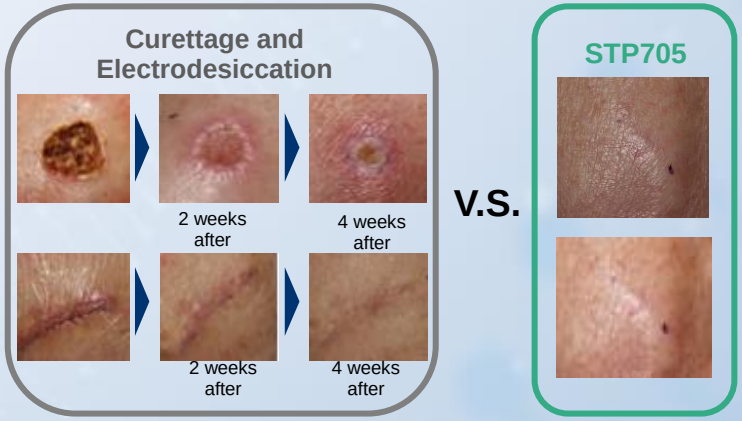
Comparison between current treatment options and STP705 treatment

- Surgery, curettage and electrodesiccation are the cornerstone treatments of NMSC. However, they have higher risk of infection, bleeding and will leave scars on skin
- Non-surgical treatments(e.g. topical) can be considered for low-risk NMSC, but generally they are less effective
- **Appearance remains one of the key needs** in NMSC treatment and has a significant impact on patient preference, especially for patients with lesions in the head or neck

Pre-Treatment



End of treatment



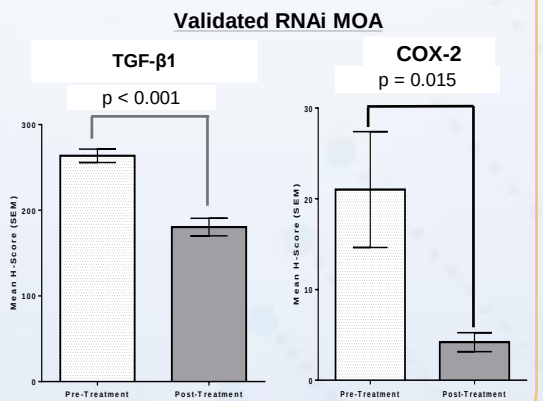
STP705 - Data Sets Support Anti-Tumor MOA for isSCC

Target-Validation

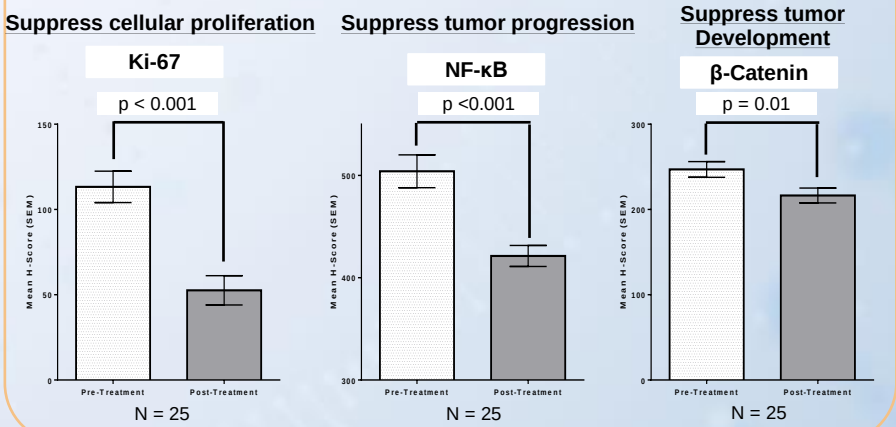
Knockdown of TGF-β1 and COX-2 was validated by RT-PCR following tissue sample collection

Knockdown tumor growth associated targets was validated by RT-PCR following tissue sample collection

Silencing of TGF-ß1 and COX-2 Expression by STP705



Suppression of multiple cancer related factors



Knockdown of TGF-β1 and COX-2 resulted in increased T-cell infiltration to tumors, enhancing killing of tumor cells by the immune system

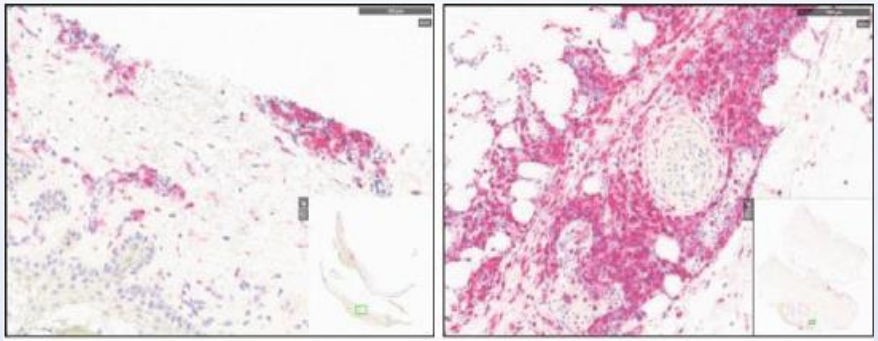
STP705 - Data Sets Support Anti-Tumor MOA for isSCC

Target-Validation

Knockdown of TGF-β1 and COX-2 was validated by RT-PCR following tissue sample collection

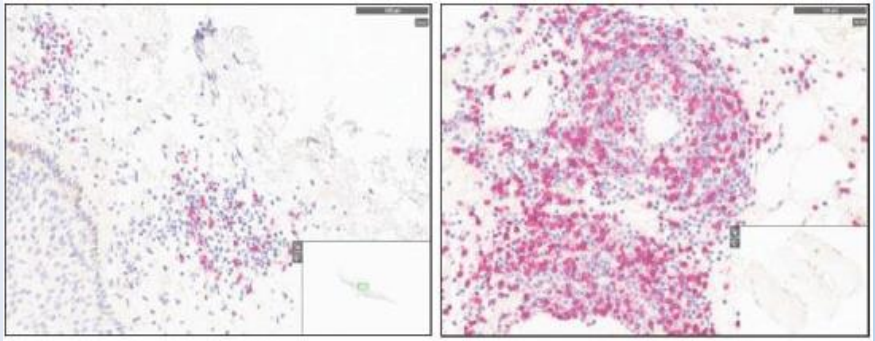
Knockdown tumor growth associated targets was validated by RT-PCR following tissue sample collection

Increased CD4 + T-Cell infiltration



Pre-Treatment | Post-Treatment

Increased CD8 + T-Cell infiltration



Pre-Treatment | Post-Treatment

Knockdown of TGF-β1 and COX-2 resulted in increased T-cell infiltration to tumors, enhancing killing of tumor cells by the immune system

Effectiveness of Treatment Published in Clinical Journal

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Safety and Efficacy of TGF-β1/COX-2 Silencing Therapeutic in Adults With Cutaneous Squamous Cell Carcinoma In Situ

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ABSTRACT

This single-center, open label, dose escalation cohort study evaluated the safety and efficacy of various doses of intralesional injections of TGF-β1/COX-2 combined with histidine-lysine polypeptide (siRNA/HKP) nanoparticle silencing therapeutic in patients with cutaneous in situ squamous cell carcinoma. Twenty-five patients (mean age: 67, SD: 10 years; 52% men) with cutaneous in situ squamous cell carcinoma participated. TGF-β1/COX-2 siRNA/HKP nanoparticle therapeutic was injected weekly for up to 6 weeks based on the following dosing cohorts: 10 µg/treatment, 20 µg/treatment, 30 µg/treatment, 60 µg/treatment, and 120 µg/treatment. The primary endpoint was the proportion of subjects with complete histological clearance. Also evaluated were the incidence/severity of treatment emergent adverse events and serious adverse events and incidence/severity of Local Skin Response. Twenty-five subjects received the TGF-β1/COX-2 siRNA/HKP nanoparticle therapeutic; 19 (76%) achieved histological clearance. In the 30 µg/treatment group and 60 µg/treatment group, percent cleared was 80% and 100%, respectively. Five subjects had 7 adverse events. There were no severe or serious adverse events; none led to treatment discontinuation, study interruption, or were related to the investigational product. Local skin response was none to minimal in most subjects, with improvement observed in the 10 µg/treatment, 20 µg/treatment, 30 µg/treatment, and 60 µg/treatment cohorts. Intralesional TGF-β1/COX-2 siRNA/HKP nanoparticle therapeutic injections appear to be noninvasive, safe, and efficacious in treating cutaneous in situ squamous cell carcinoma. The recommended doses for future study of the investigational product are 30 µg/treatment and 60 µg/treatment.

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FIGURE 1A. The pre-treatment, squamous cell carcinoma in-situ lesion on the left radial dorsal hand of a 45-year old, white female patient is pictured. The biopsy at the time of screening confirmed the presence of squamous cell carcinoma in-situ before treatment with 60µg/treatment of TGF-β1/COX-2 siRNA/histidine-lysine polypeptide therapeutic. The local skin response score was 3, with visible erythema surrounding the lesion.

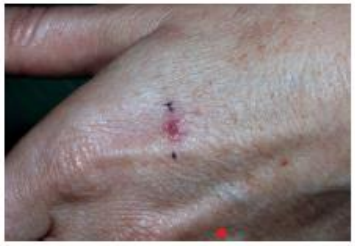
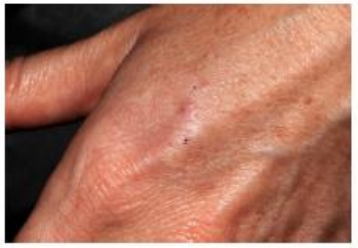


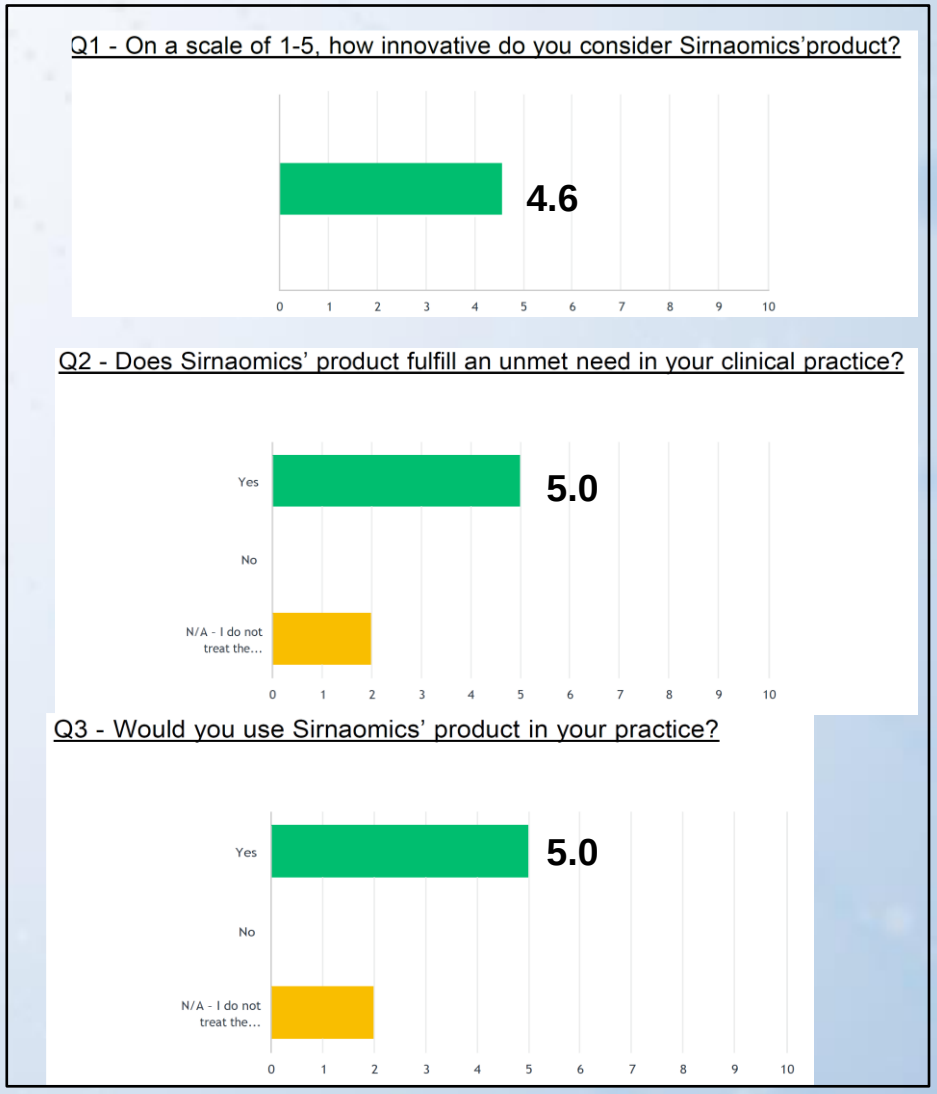
FIGURE 1B. T post-treatment lesion site of the same patient after 6 weeks of treatment with 60 µg/treatment of TGF-β1/COX-2 siRNA/histidine-lysine polypeptide nanoparticle therapeutic is pictured. Complete histological (margins free of tumor) and clinical clearance of squamous cell carcinoma in-situ is observed, and the final local skin response score was 2.



female patient in the 60 µg/treatment group that was cleared of isSCC after 6 weeks of treatment with TGF-β1/COX-2 siRNA/HKP nanoparticle therapeutic.

Result on STP705 isSCC Recognized by Peers

Survey: In a survey of nearly 2,000 dermatology clinicians, STP705 scored 4.6, 5.0 and 5.0 on a scale of 1 to 5, making it one of the top three products!



STP705 - isSCC Positive Phase IIb Interim Data

Professor Mark Nestor MD/PhD, University of Miami

- Positive Phase IIb Clinical Readouts for isSCC treatment
- Overall, **78%** of subjects across all groups (32 subjects) achieved Histological Clearance
- **Lowest dosage in study is identified at Cohort A (30 µg/ml) which achieved 89% histological clearance**
- **No significant cutaneous skin reactions** and **no** treatment related **AE's or SAE's**, Skin Response Scores improved in 4/5 dosing cohorts and there were no dose limited toxicities noted in the study population

- The two-part, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy, administered as an intralesional injection in subjects with isSCC
- In the part-one of the study, treated 32 patients with 30 µg/ml, 60 µg/ml and 90 µg/ml of STP705 and 12 patients with 0 µg/ml placebo weekly for 6 week repeated dosing. This interim data is specifically for the study with total of 44 patients

	Histological Clearance
Cohort A: 30 µg/ml N= 9	**89%**
Cohort B: 60 µg/ml N= 12	**75%**
Cohort C: 90 µg/ml N= 11	**73%**
Cohort D: placebo group N= 12	**58%**
Overall Treatment Result	**78%**

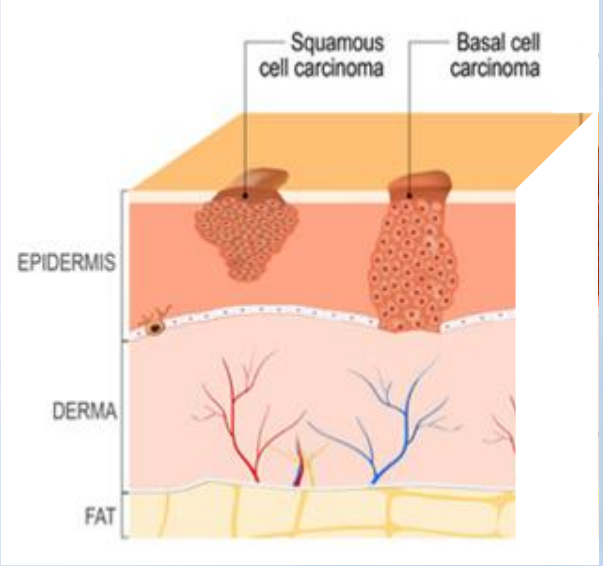
Formulating communication with the U.S. FDA for late-stage clinical Study

STP705 - Clinical Phase II Study for Treatment of BCC

Phase II in Progress

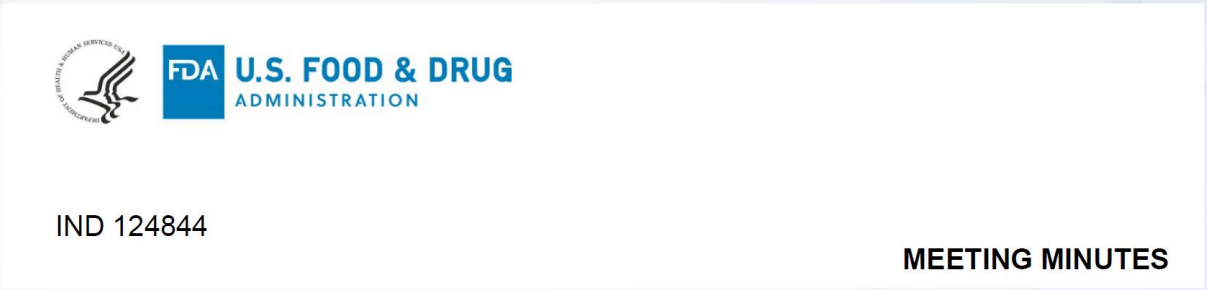
	Cohort A: 30 µg (N=5)	Cohort B: 60 µg (N=5)	Cohort C: 90 µg (N=5)	Cohort D: 120 µg (N=5)	Cohort E: 180 µg (N=5)	Cohort F: 240 µg (N=5)
Histological Clearance	1/5 **20%**	3/5 **60%**	3/5 **60%**	2/5 **40%**	5/5 **100%**	3/5 **60%**
Average Skin Response Scores						
Pre-treatment	3.2	2.8	2.6	Scores not reported until final report		
Post-treatment	2.4	2.6	2.6			

- Phase II, open label dose escalation study designed to evaluate the safety, tolerability and efficacy of various doses of STP705 administered as localized injection in patients with BCC. Total of 25 subjects which is divided equally among 5 cohorts (30, 60, 90, 120 and 180 µg dose level)
- Interim data achieves **100% response rate** in the 180 µg dose level. The data showed improved or stable cosmetic result with an excellent safety profile (**no adverse events**) **and no significant cutaneous skin reactions**
- The additional completed group 6 (240 µg dose level) also showed **positive (60% complete clearance) results**
- Looking forward to **mirror the promising data** - the potential to be an alternative to patients with BCC and other non-melanoma skin cancers who have an urgent need for new treatments



Reached optimum dosage, ready to move on to next phase of the study

STP705 - isSCC Advance to Late-Stage Study


U.S. FOOD & DRUG ADMINISTRATION

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MEETING MINUTES

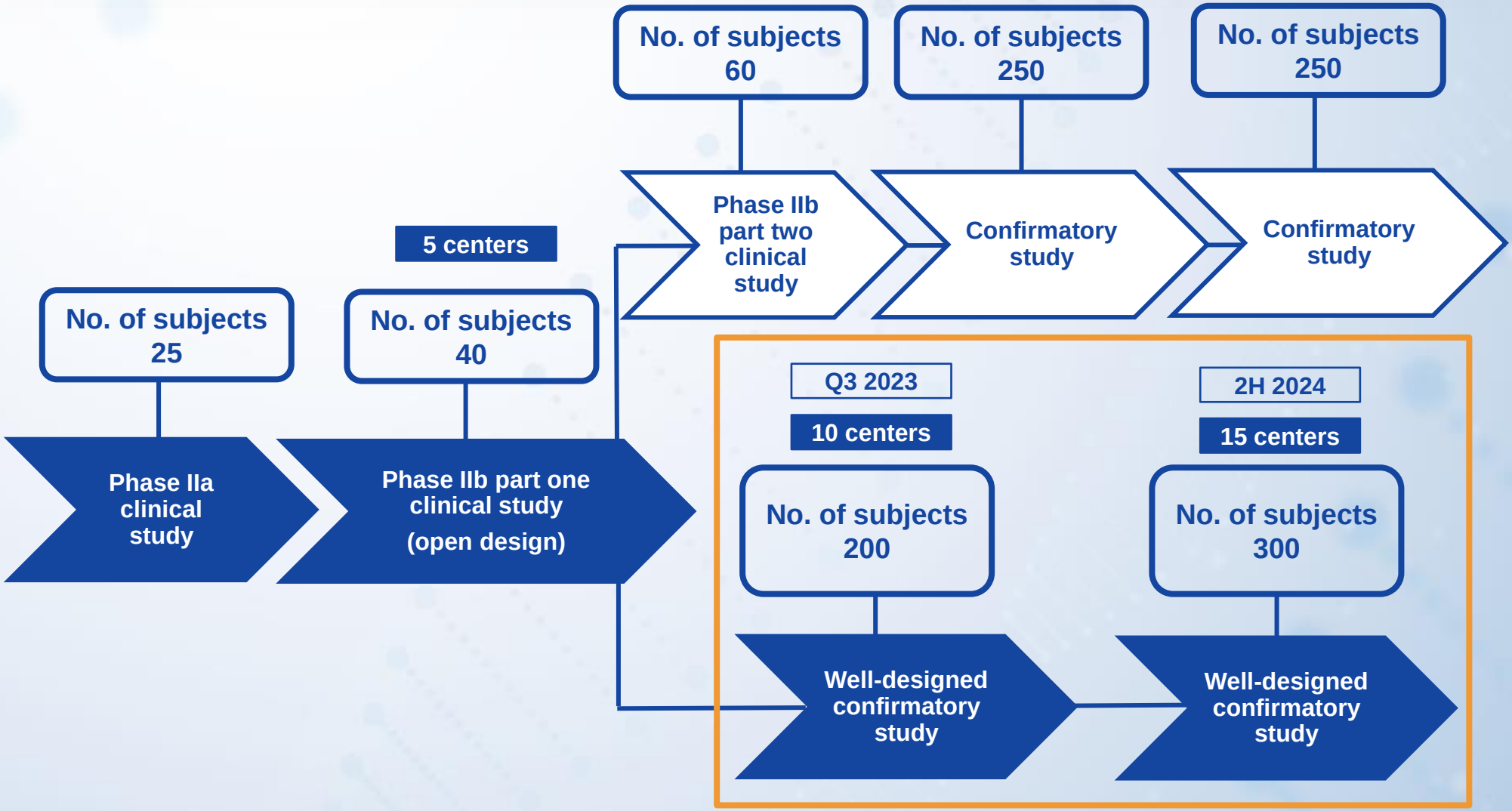
Through communication with the U.S. FDA's scheduled Class B meeting (May 8, 2023) and the guidance provided in the legally binding minutes (June 8, 2023), Sirnaomics has confirmed the following basic protocol for **addressing and advancing the Phase III clinical trial** of STP705 for isSCC.

Sirnaomics is **well-positioned** currently to advance STP705 into a **confirmatory clinical study** for treatment of Squamous Cell Carcinoma in situ (isSCC).

We are preparing to move forward in 2023 with a **well-designed** single dosage study as a **sub-group** of subjects in a large Phase III clinical study.

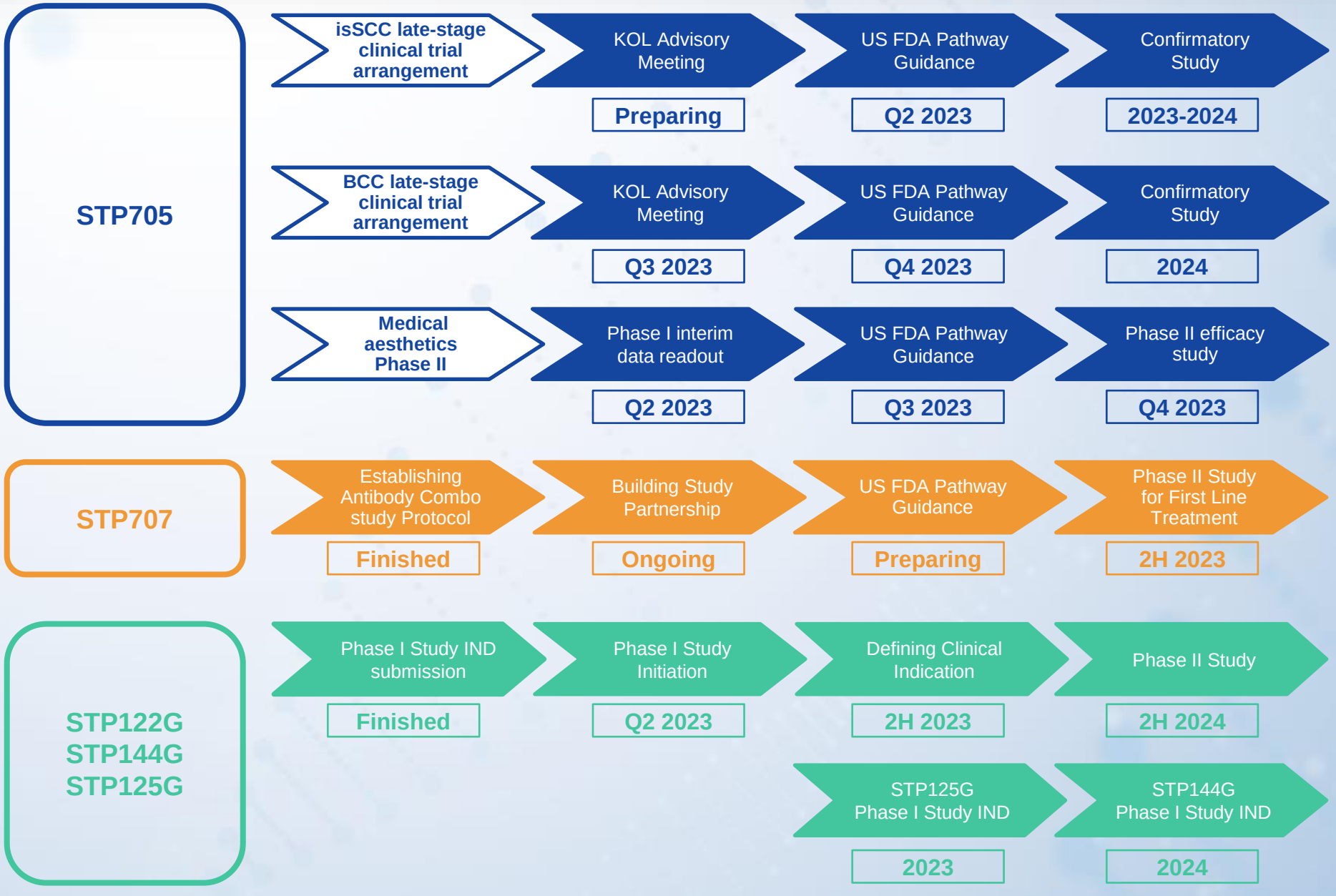
The positive results would provide the basis for completion of this large registration Phase III trial.

STP705 - isSCC Late-Stage Protocol



A clearer pathway through regulatory requirements for future medicine

Full Speed Ahead - Future Milestones



sirnaomics
Advancing RNAi Therapeutics

Q&A