Preliminary Competitive Intelligence Landscape report for Duchenne Muscular Dystrophy

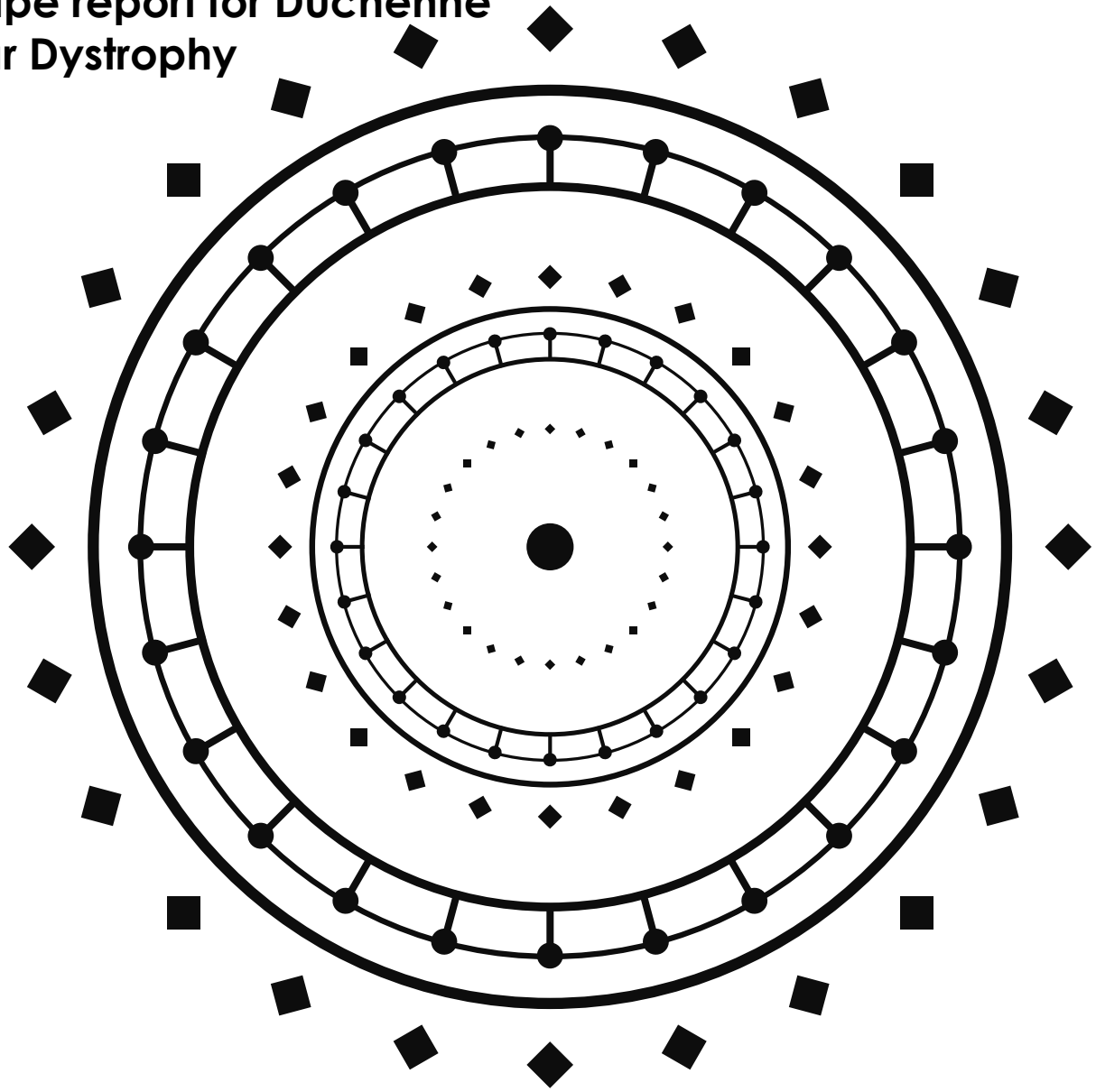


Table of Content

PharmaACE help clients in decision making with thorough intelligence and answering key business questions

How will the new regulatory policies impact the industry?

Which products are likely to pose high competition to my drug?

Who are my target/ key customers?

Who are the vendors for my key competitors?

Which products should I start developing to be the first in market for a therapy area?

What are my competitor's strategy to differentiate their product in the market?

When new entrants will be entering in the market?

Who will be my future competitors?

CI Team provides key information and insights to their clients, enabling them to stay ahead of the competition and minimize/eliminate business risks

Duchenne Muscular Dystrophy (DMD) is a rare progressive genetic disorder that is caused due to mutation in DMD gene commonly affecting males

Duchenne Muscular Dystrophy

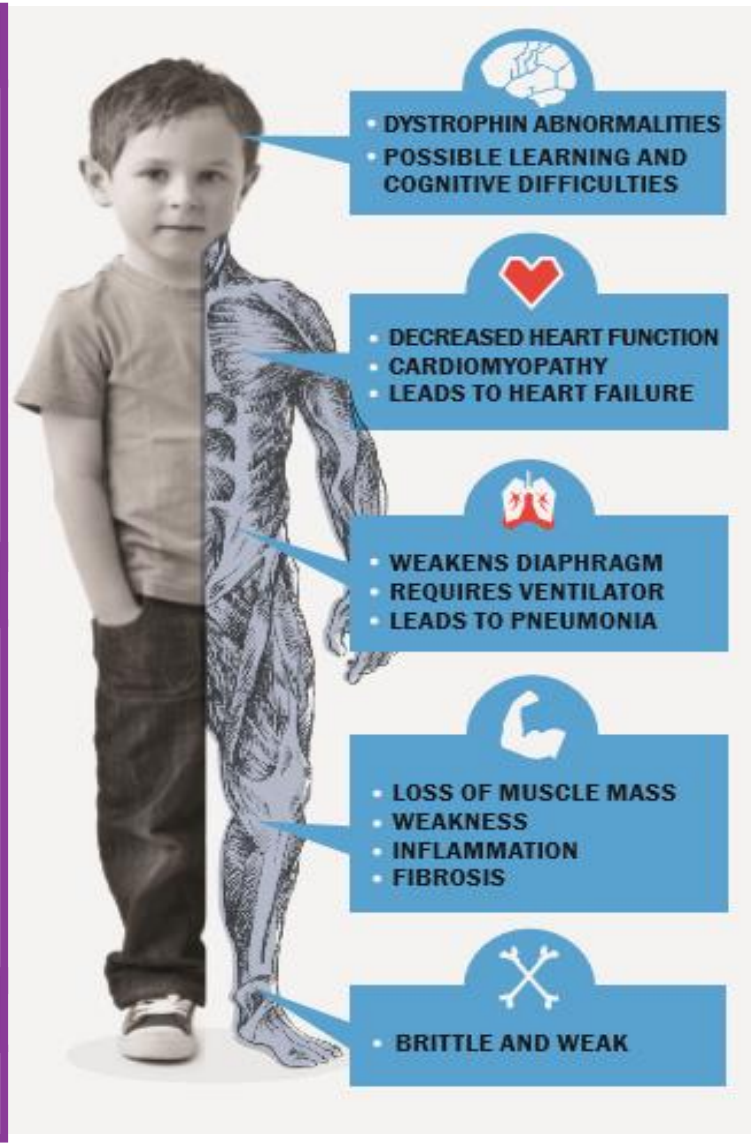
- Inherited X-linked, muscle-wasting disorder
- Characterized by progressive loss of mobility, pulmonary insufficiency, cardiomyopathy and premature death
- Patients with DMD are usually diagnosed before age of 5
- By the age of 12 they start using wheelchair and most don't survive their mid 20's with average life expectancy of ~26yrs

Symptoms

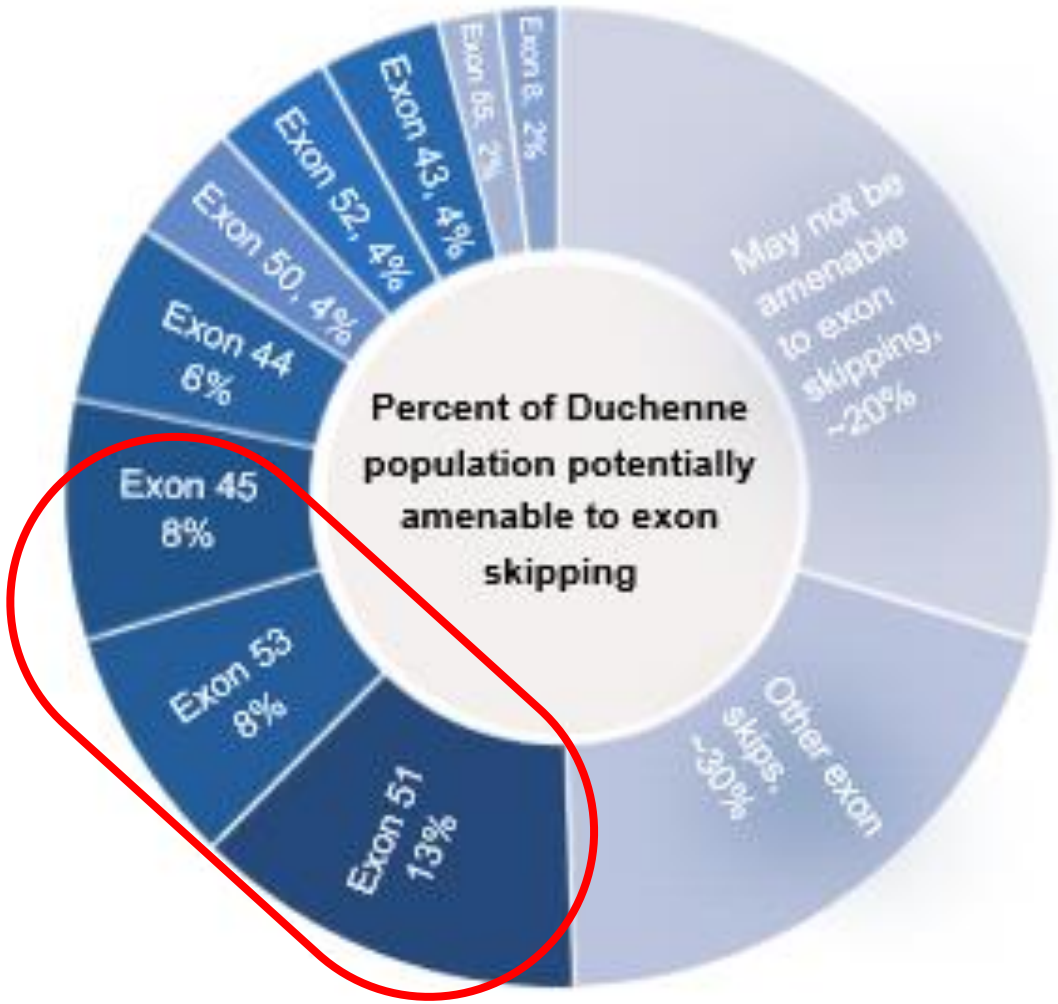
- Calf muscle hypertrophy
- Cardiomyopathy
- Cognitive impairment
- Delayed speech and language development
- Elevated serum creatine phosphokinase

Epidemiology

12000 boys in U.S., 300k boys worldwide



The majority of Duchenne patients are thought to be potentially amenable to Exon Skipping, with exon 45, 51, 53 skipping, target the highest prevalence



Exon skipping is a potential treatment approach to correct and restore production of dystophin

- For specific genetic mutations it allows the body to make a shorter, usable dystophin
- Exon skipping is not a cure for Duchenne, but it may make the effects less severe
- No single drug is believed to rescue all mutations
- It is estimated that 13% of Duchenne patients have a mutation amenable to skipping exon 51
- Exon skipping may eventually apply to 60-80% of Duchenne patients

Research Objectives

1. To identify the marketed and Pipeline products for Duchenne muscular dystrophy and based on their attributes to identify the impact of entry of product in market

2. To suggest the novel delivery technologies options available to deliver proteins and peptides having 24 or more amino acids and can be given to DMD patients

Research Methodology

Study Type

1

Descriptive Research

Data Collection

2

Secondary Sources

Sources

3

- Clinical trial
- Company Web
- SEC
- Adis Insights

Location

4

World Wide (Focus: USA)

Review of Literature (1/2)

Straub V., Strehle EM. (2015) conducted a study on topic “Recent advances in the management of Duchenne Muscular Dystrophy”. Duchenne muscular dystrophy (DMD) is the commonest inherited neuromuscular disorder of childhood and mainly affects males. Over the course of the last century, the average life expectancy of these patients has doubled and now stands at ~25 years. This progress has been made possible through advances in the diagnosis, treatment and long-term care of patients with DMD. Basic and clinical research, national and international scientific networks, and parent and patient support groups have all contributed to achieving this goal. The advent of molecular genetic therapies and personalised medicine has opened up new avenues and raised hopes that one day a cure for this debilitating orphan disease will be found. The main purpose of this short review is to enable paediatricians to have informed discussions with parents of boys with DMD about recent scientific advances affecting their child’s clinical care

Review of Literature (2/2)

Leadley RM., Armstrong N. et. all. (2017) titled as “The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review” defined the abstract as Duchenne Muscular Dystrophy (DMD) is a rapidly progressive, lethal neuromuscular disorder, present from birth, which occurs almost exclusively in males. Author have reviewed contemporary evidence of burden, epidemiology, illness costs and treatment patterns of DMD. This systematic review adhered to published methods with information also sought from the web and contacting registries. The population of interest was individuals with clearly defined DMD or their careers.

DMD approved marketed therapies: out of 3, two drugs are oral formulations and are of PTC Therapeutics

01

PTC THERAPEUTICS™

Translarna

Ataluren

Oral Formulation

02

SAREPTA THERAPEUTICS

Exondys 51

Eteplirsen

Intravenous Formulation

03

PTC THERAPEUTICS™

Emflaza

Deflazacort

Oral Formulation

Mechanism of Action / Pharma Class
Protein synthesis stimulants (Gene Therapy)
Exon Skipping
Steroid receptor agonist

DMD 'Late Clinical Stage' Pipeline Landscape: In the U.S., There are x6 industry-sponsored assets in Phase III and x2 in Phase II/III clinical development

Phase II/Phase III

BMS-986089 /RG6206
BMS/Roche

Epigallocatechin-Gallate
Charite University, Berlin, Germany

Bisoprolol Fumarate with ACE inhibitors
Peking Union Medical College Hospital, China

Suvodirsen (WVE-210201)
WaVe life Sciences
Phase 2/3 initiated. Phase 1 completed on March 06, 2019

Phase III

ITF 2357/Givinostat
Italfarmaco

SRP-4045
Sarepta
Plans to file NDA in mid 2019

SRP-4053/golodirsen
Sarepta

Idebenone/Puldysa/Raxone
Santhera
Intend to file CMA in H2 2019

L-citrulline and Metformin
University Hospital, Switzerland

CAT-1004 (Edasalonexent)
Catabasis Pharma
Intend to submit NDA in early 2021

Translarna/ataluren
PTC Therapeutics
NDA rejected. Resubmission in early 2020

Tamoxifen (TAMDMD)
University Hospital, Switzerland

Nebivolol
Assistance Publique - Hôpitaux de Paris, France

Pre-registration

EXONDYS 51 (eteplirsen)
Sarepta Therapeutics

SRP-4053/golodirsen
Sarepta Therapeutics
FDA action date is Aug 19, 2019

Mechanism of Action / Pharma Class
AMP activated protein kinase stimulants
Histone deacetylase inhibitor
Reactive oxygen species inhibitors
Steroid receptor agonist
Exon Skipping
Protein synthesis stimulants (Gene Therapy)
Myostatin inhibitors
Estrogen receptor antagonists
Beta 1 adrenergic receptor antagonists
AMP activated protein kinase stimulants/ Amino Acis replacements
NF-kappa B inhibitors

Trials on patients between 4-8 years of age

Orphan Drug Designation

Non-industrial trial

Geography

US · Ex-NA · Canada · Unknown

ROA

Sub-cutaneous · Intramuscular · Oral · Intracoronary · Intrathecal · Unknown · IV

DMD 'Early Clinical Stage' Pipeline is very crowded, with 27 assets identified

Phase I

- **ARM 210** — *ARMGO Pharma*
- **Rimeporide** — *Merck Serono, EU*
- **Tamoxifen** — *Hadassah Medical Organization, Israel*
- **Spironolactone** — *Nationwide Children's Hospital*
- **G-CSF/Filgrastim** — *Medical University of Bialystok, Poland*
- **MA-0211** — *Mitobridge*
- **PF-06939926** — *Pfizer*
- **BLS-M22** — *BioLeaders Corp. Korea*

Phase I / Phase II

- **DS-5141** — *Daiichi Sankyo, Japan*
- **Epicatechin** — *Cardero Therapeutics*
- **AAV1-Follistatin** — *Milo Biotechnology*
- **Myoblast transplantation** — *CHU de Quebec-Universite Laval*
- **Bone Marrow-Derived Autologous Stem Cells** — *Stem Cells Arabia*
- **rAAVrh74.MCK.GALGT2** — *Sarepta Therapeutics*
- **SGT-001*** — *Solid Biosciences/Seismic*
- **SRP-5051** — *Sarepta*

Phase II

- **NS-065/NCNP-01/Viltolarsen** — *Nippon Shinyaku*
- **TAS 205** — *Taiho Japan*
- **CAP 1002** — *Capricor*
- **ATL1102** — *Antisense Therapeutics,Australia*
- **Ifetroban** — *Cumberland Pharmaceuticals*
- **FG-3019** (Pamrevlumab) — *FibroGen*
- **Prednisolone** — *Washington University School of Medicine*
- **MNK-1411/ Synacthen Depot** — *Mallinckrodt*
- **VBP-15** (Vamorolone) — *ReveraGen BioPharma Registrational trial*
- **SRP-9001** — *Sarepta*
- **P-188** (Poloxamer) — *Phrixus Pharmaceuticals, Inc.*

Trials on patients between 4-8 years of age

Non-industrial trial

Orphan Drug Designation

Mechanism of Action / Pharma Class

- Connective tissue GH inhibitors
- Anti-myotatin
- Estrogen receptor antagonists
- Sodium hydrogen antiporter inh.
- Cell Replacements
- Granulocyte colony factor stimulant
- Dystrophin expression stimulants
- Melanocortin receptor agonist
- Ryanodine receptor Ca release channel modulators
- Gene delivery
- Blood Cell modulators
- Prostaglandin synthase inhibitors
- PPAR delta
- Mitochondrial protein modulators
- Myostatin inhibitors
- Glucocorticoid receptor antagonist
- Antisense inhibitor of CD49d
- Exon-skipping
- Aldosterone antagonist
- Thromboxane A2 receptor antagonists

Geography

- US
- Ex-NA
- Canada
- Unknown

ROA

- Sub-cutaneous
- Intramuscular
- Oral
- Intracoronary
- Intrathecal
- Unknown
- IV

DMD 'Preclinical' Pipeline Landscape: ~40% of all identified assets (11/28) focus on 'Exon Skipping' to treat DMD

Preclinical

- **TXA127** — *Tarix Pharmaceuticals*
- **AT-300** — *Akashi Therapeutics*
- **DMD Therapy** — *Fulcrum Therapeutics*
- **Muscle stem/progenitor cells** — *University of Minnesota Medical School*
- **AT702** — *Audentes Therapeutics*
- **AT751** — *Audentes Therapeutics*
- **SRP-5053** — *Sarepta Therapeutics*
- **SRP-5050** — *Sarepta Therapeutics*
- **SRP-5044** — *Sarepta Therapeutics*
- **WVE-N531** - *Exons 53* — *Wave Life Sciences* — *Top line data is expected H2 2020*
- **DMD therapies** - *Exons 44, 45, 52, 54, 55* — *Wave Life Sciences*
- **CRISPR/CAS9*** — *Sarepta/Duke University*
- **AT753** — *Audentes Therapeutics*
- **SRP-5045** — *Sarepta Therapeutics*
- **SRP-5052** — *Sarepta Therapeutics*
- **CRISPR gene editing** — *Exonics Therapeutics*
- **MSI-1436** (trodusquemine) — *Novo Biosciences*
- **Jagged1 protein** — *Children's Hospital in Boston*
- **DMD Program** — *Genethon*
- **TVN-102** — *Tivorsan Pharma*
- **IB-DMD** (Andrographolide) — *InnoBioscience*
- **IL-4 nanoparticles** — *Wyss Institute at Harvard*
- **EGFR producing Gene** — *University of Ottawa*
- **SPY-DYS** — *MyoGene Bio*
- **DMD therapy for patients with mutations in exons 44 and 45** — *Avidity Biosciences*
- **Engineered Exosomes** — *Evox Therapeutics*
- **Taurine** — *The University of Western Australia*
- **Exon skipping or micro-dystrophin gene therapy** — *Binghamton University*
- **CRISPR gene editing*** — *University of Missouri School of Medicine,*
- **CRISPR gene editing*** — *UT Southwestern Medical Centre*

Disclaimer: This is not an exhaustive list of assets in 'preclinical' stage

Non-industrial trial

Orphan Drug Designation

Geography

US | Ex-NA | Unknown | Canada

ROA

Sub-cutaneous | Intramuscular | Oral | Intracoronary | Intrathecal | Unknown | IV

Mechanism of Action / Pharma Class

- *Proto-oncogene protein c-mas-1 agonists*
- *Anti-inflammatory cytokine*
- *Antibody oligonucleotide conjugate*
- *Protein tyrosine phosphatase inh.*
- *Utrophin activators*
- *Myostatin inhibitors*
- *NF-kappa B inhibitors*
- *Unknown*
- *Calcium channel inhibitor*
- *Gene therapy*
- *Exon Skipping*
- *Amino acid*
- *Cell replacements*

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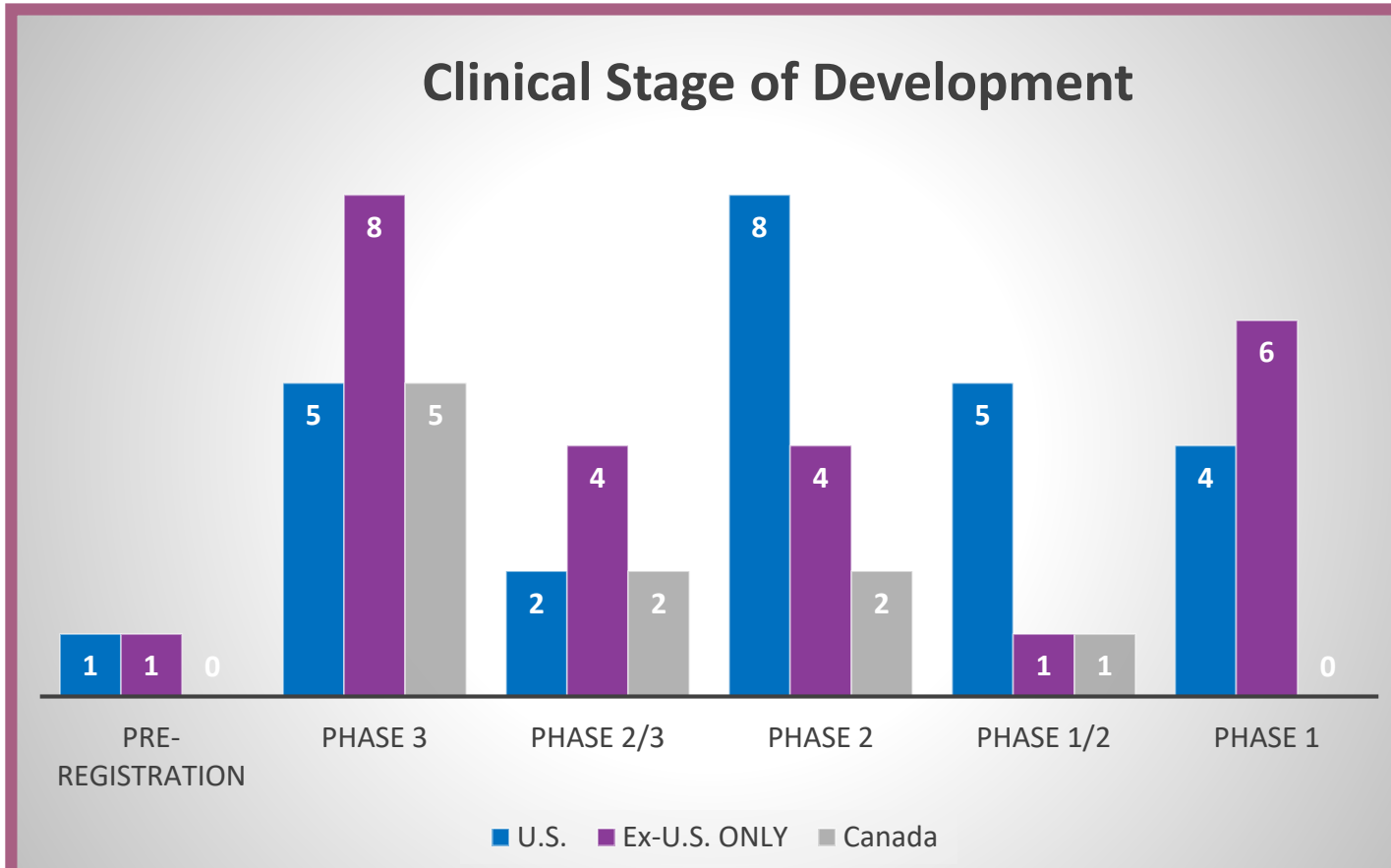
Overall Summary of Clinical stage of development for Duchenne muscular dystrophy



Total number of ongoing trials:

- **U.S.: 25**
- **Ex-NA: 24**
- **Canada: 10**

- Maximum number of trials ongoing are in Phase 3 followed by Phase 2
- Exondys 51 & Golodirsen are the 2 drugs which are going to launch soon for DMD as the molecules are in Pre-registration Phase

Some trial are common in U.S. and Ex U.S. and considered in both

Attribute Analysis Of High Impact Pipeline Assets: MNK-1411, CAT-1004, and VBP-15 could become first line treatment options, VBP-15 would be the highest threat among all of them

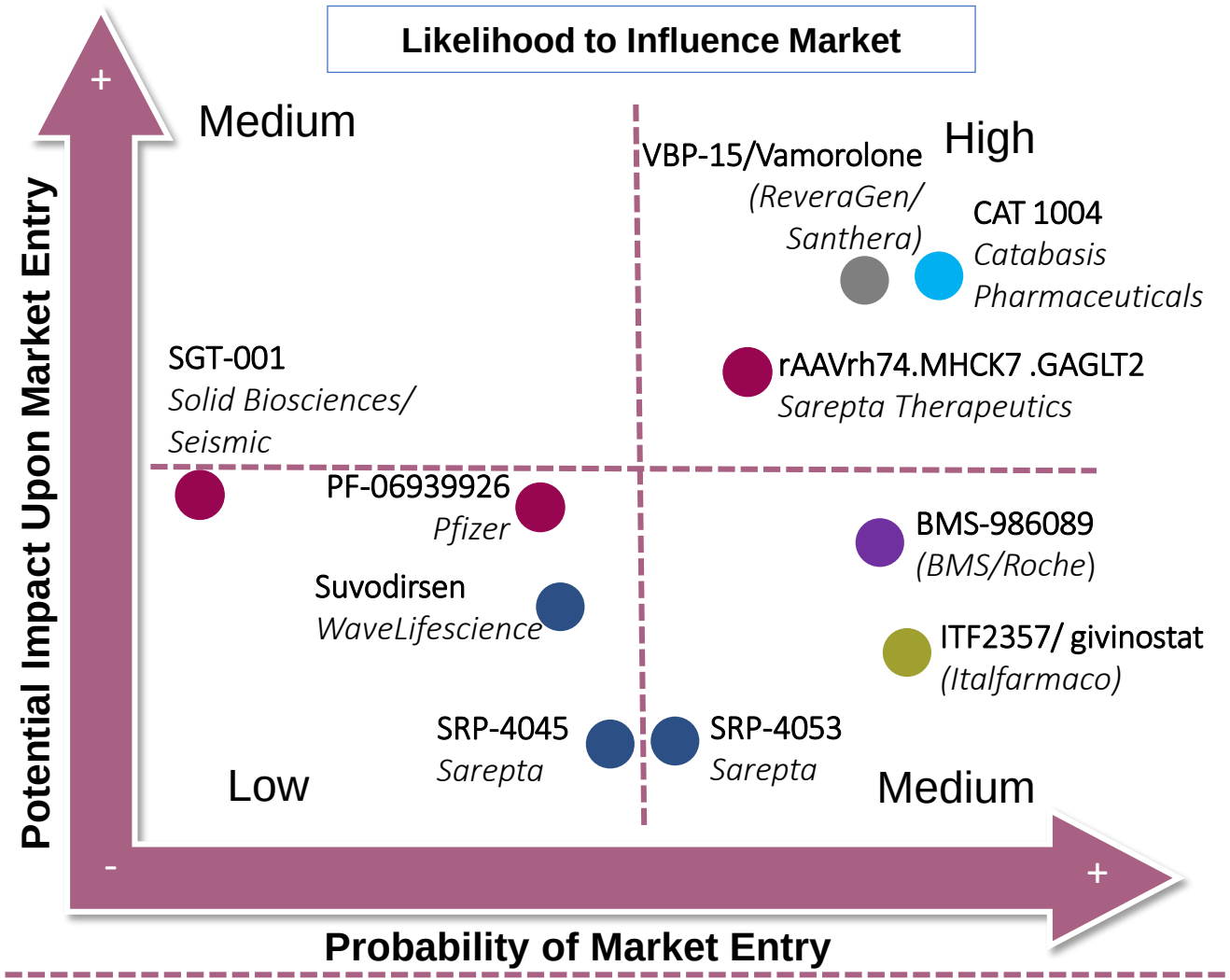
Attributes	MNK-1411 (Mallinckrodt)	CAT-1004/ Edasalonexent (Catabasis)	VBP-15/ Vamorolone (ReveraGen/Idorsia/ Santhera)	rAAVrh74.MHCK7.GAGLT2 (Sarepta Therapeutics)
MoA	Melanocortin receptor agonist	NF-kappa B inhibitors	Glucocorticoid receptor antagonist	Gene Delivery
Phase	Phase 2 (NCT03400852) Recruiting, Dosed first patient in Aug 2018	Phase 3 PolarisDMD pivotal trial (NCT03703882) recruitment ongoing	Phase 2b (NCT03439670), (recruiting)	Phase 1/2a (NCT03375164). In 2019, Sarepta plans to commence a confirmatory trial with commercial material
Patient number (n)	132	125	120	24
Region	U.S., Ex-NA	U.S., Canada, Ex-NA	U.S., Canada, Ex-NA	U.S.
RoA	Subcutaneous	Oral	Oral	Intravenous
Dosing	Twice a week	Three times a day	QD	One-time therapy
Orphan Drug Designation	Yes (U.S., EU)	Yes (U.S., EU)	Yes (U.S., EU)	No
Fast track designation	Yes	Yes	Yes	No
Est. U.S. Launch	Q4-2024	Q3-2021	H2 2021	Q1-2022

Relative Attribute Comparison

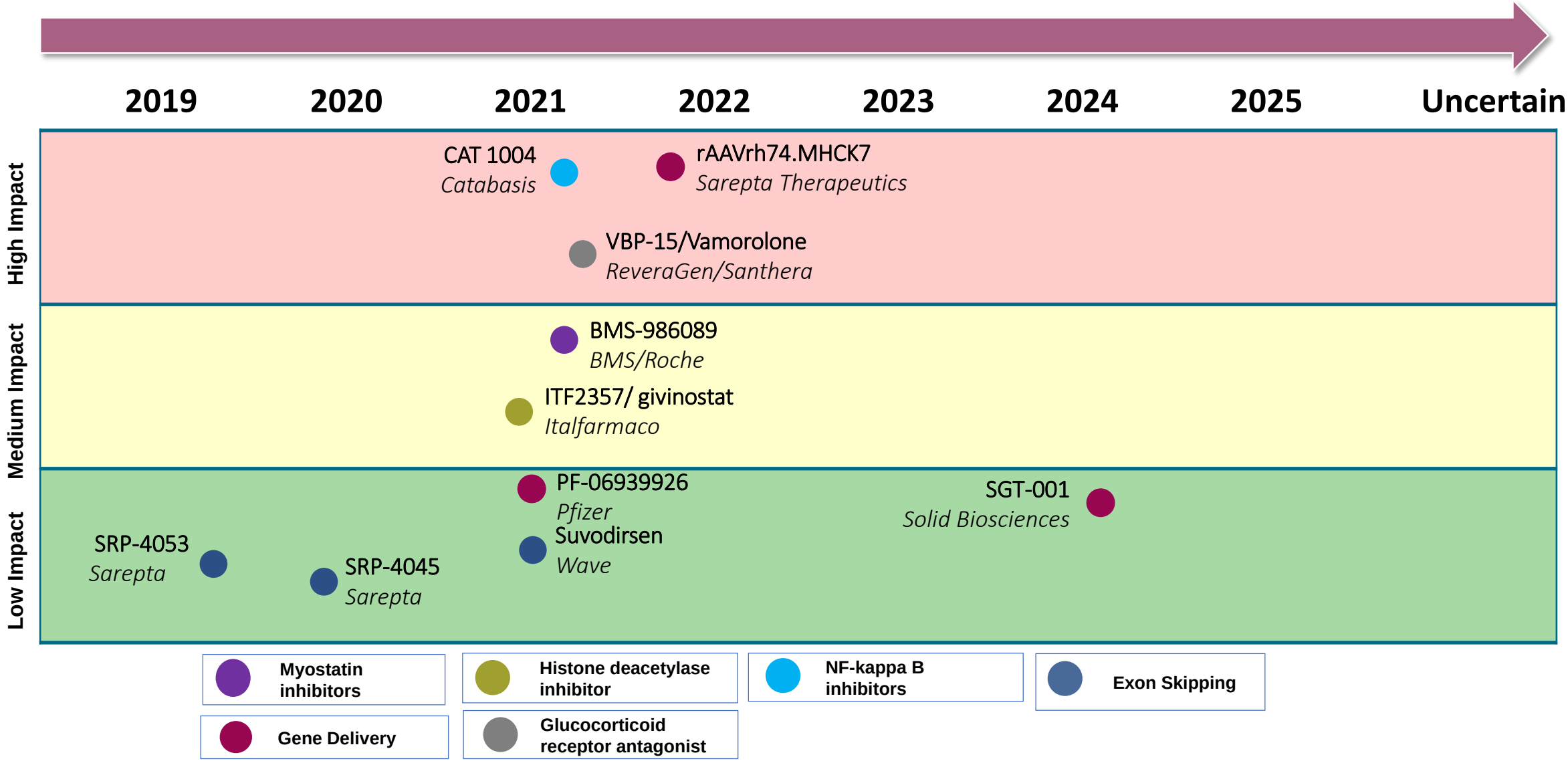
Strongly favored | Less favored | Not Attractive

Assessment of Future Impacts to DMD Market

Specific to Phase II + with 4-8 Year Patient Population



Potential Order of Entry for DMD Pipeline Products



Attribute Analysis of delivery technologies that can be explored to deliver Proteins and peptides

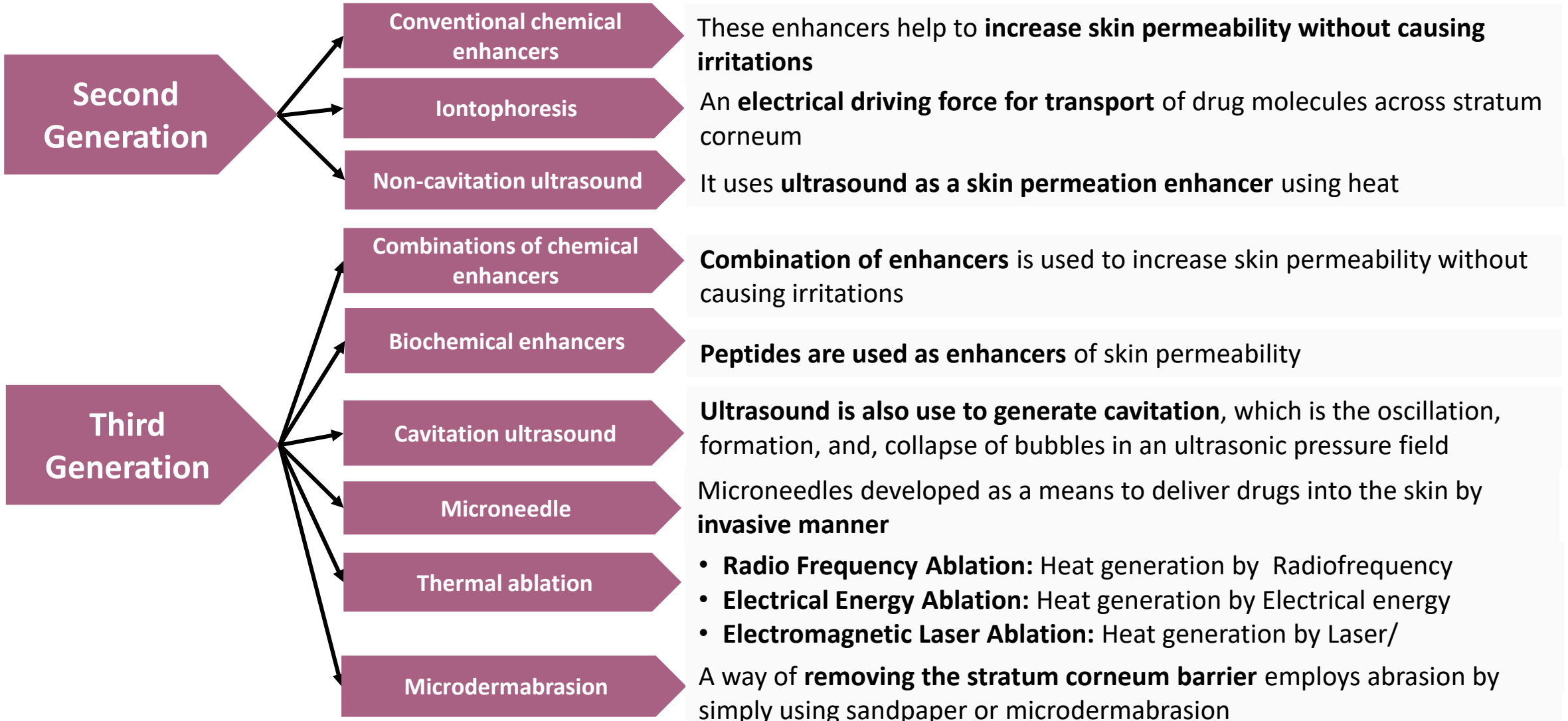
Pulmonary and sublingual deliveries have not been developed for controlled/sustained release of high molecular weight drugs

	Implantable Pumps	Injectors	Transdermal	Pulmonary	Sublingual	Oral
Formulation change would be required	✗	✗	✗	✓	✓	✓
Suitable Drug Carriers	Microparticles, Nanoparticles, Hydrogels	Microparticles, Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels	Nanoparticles, Hydrogels
Delivery route	Implants or patch	SC, IM, ID	Transdermal patches	Inhalation	Buccal (sublingual)	Oral
Controlled/ sustained release	✓	✓	✓	✗	✗	✓
Developmental Cost	↑ $	↑ $	↓ $	↑ $	↓ $	↓ $
Patient Compliance	High	Medium	High	High	High	High
Examples	DUROS device	Bydureon BCise	Viador	Technosphere technology platform has also been used to deliver salmon calcitonin	Exenatide (under development)	Robotic pill of insulin (under development)

Types of delivery mechanisms used for transdermal patches

Delivery of drugs is primarily mediated via chemical enhancer, electrical force and heat generation

Types of transdermal delivery systems



Thermal ablation technology works on the principle of creating micropores using different forms of energies to deliver the drug

Technologies of Thermal ablation

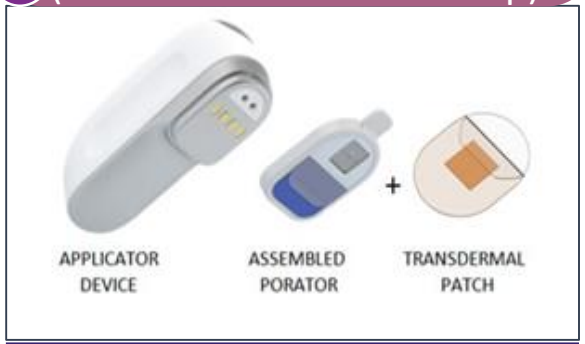
1. **P.L.E.A.S.E. Technology** (Pantech Biosolutions)

Laser/ Electromagnetic Energy

2. **Viador** (TransPharma Medical)

Radiofrequency

3. **Passport Technology** (Nitto Denko technical Corp)



Electroporation

Micropores are generated due to heat using different types of energies. The drug permeates through these micropores

- **It is a two step process wherein micropores are created using the device and then the patch is applied manually**
- **It is an automated process wherein the device is involved in both the creation of the micropores and application of the drug patch**
- **It is also an automated process but consist of two devices, an applicator and a porator, that needs to be clipped together**

iPRECIO is an implantable, programmable micro infusion pump used in small laboratory animals that allows control of infusion and drug flow rate

Novel Implantable Pump delivery Technology

- The recent availability of iPRECIO, a programmable, refillable, and implantable infusion pump which is implanted in subcutaneous space of the body
- With the use of specialized catheters, specific administration sites may be selected including ICV, intrathecal, IV, SC
- It consists of a microcontroller with associated memory, embedded software, inputs/outputs, a micro pulse stepping motor, crystal oscillators, electronic circuitry, and a battery power source. The embedded software in the microcontroller is programmed via a PC-based software platform

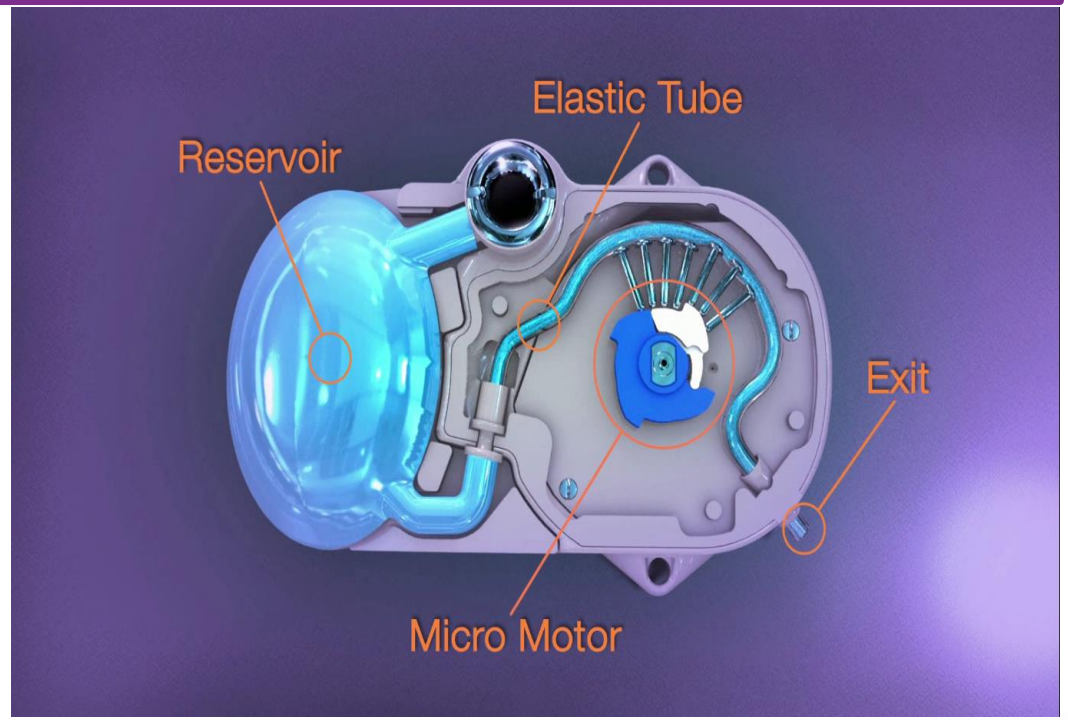
iPRECIO is equipped with battery-operated micro motor which rotates clockwise at a very slow speed and an elastic tube extended from the reservoir to the exit point for drug delivery

↓

Seven pins are pushed outwards in order to place pressure on elastic tube due to rotations of clamps attached to the motor. The fluid is displaced from elastic tube by peristalsis

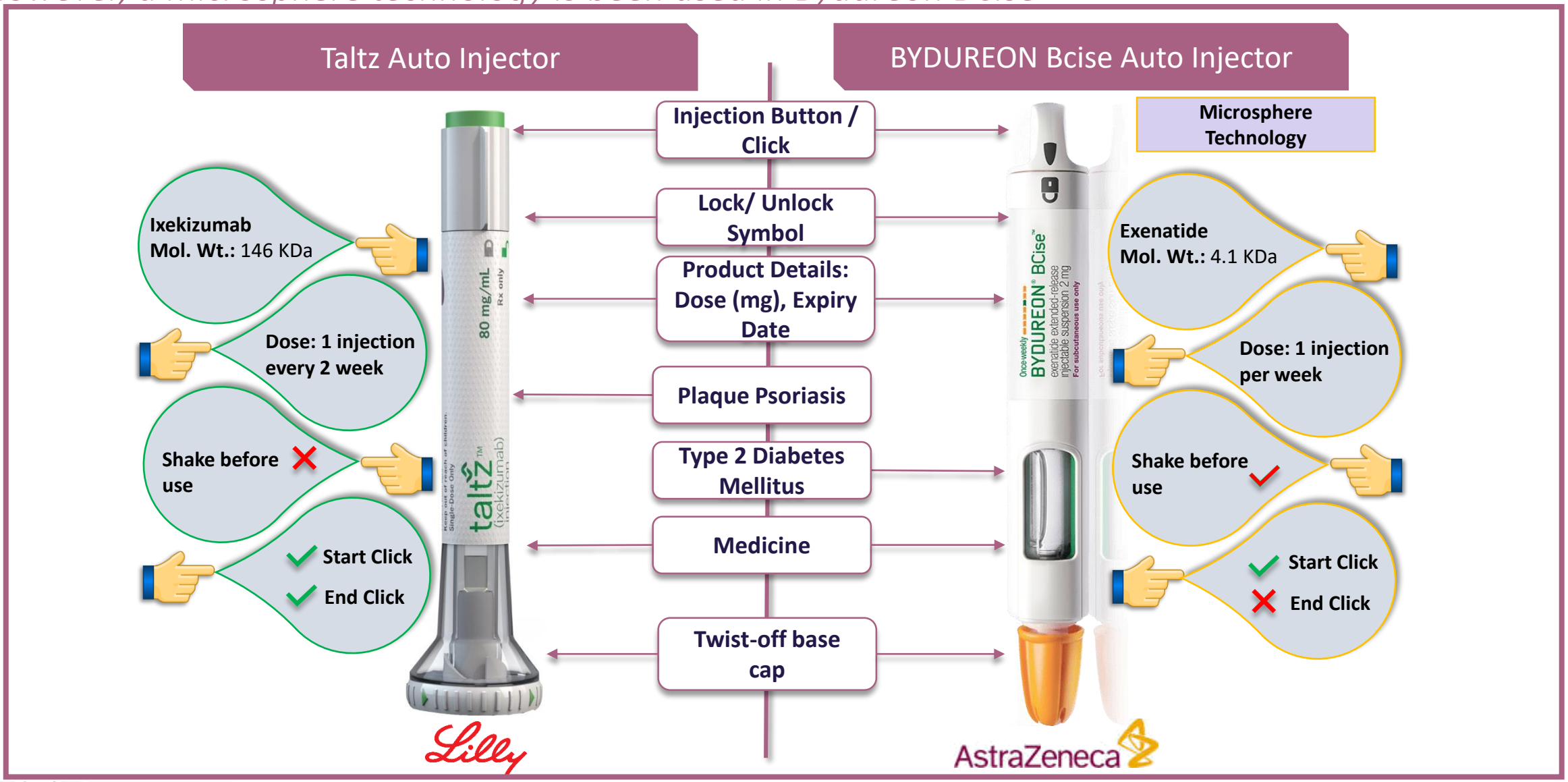
↓

The device is programmed by windows-based management software. This software helps to configure Infusion modes or flow rate modes



Both Taltz and Bydureon Bcise autoinjectors are novel with Taltz being more automated

However, a microsphere technology is been used in Bydureon BCise



Technosphere dry powder formulation delivers proteins with molecular weight ranging from 500 to 140,000 KDa

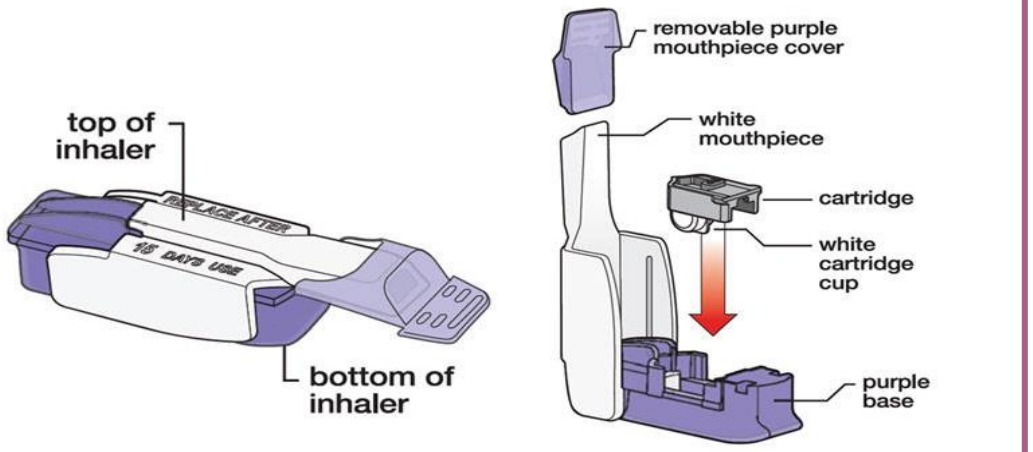
Novel Pulmonary Drug delivery technology

- MannKind's dry powder formulation technology is a versatile drug delivery platform that allows the pulmonary delivery of therapeutic agents by oral inhalation
- Drugs ranging in molecular weight from 500 to 140,000 Da have been successfully adsorbed onto Technosphere particles
- Example: AFREZZA is FDA approved rapid acting inhaled insulin indicated to improve glycaemic control in adult patients with diabetes mellitus

Technosphere insulin uses fumaryl diketopiperazine (FDKP) as a carrier which electrostatically adsorbs insulin to form microparticles → **The resulting powders have a low density and are readily dispersed from simple, patient-friendly inhalers** → **After inhalation, the powders dissolve rapidly and deliver the drug directly into the arterial circulation, bypassing the liver to provide excellent systemic exposure**

Advantages

- ✓ **Applicability to a wide variety of drugs including proteins and peptides**
- ✓ **Excellent bioavailability**
- ✓ **Rapid drug absorption that mimics intraarterial delivery**
- ✓ **Improved convenience with patient-friendly, needle-free devices**



Rani Pill is a novel oral drug delivery technology that delivers proteins & peptides with the help of Robotic Pill

Novel Oral Drug delivery technology

- Rani's "robotic" pill is a sophisticated device which incorporates a number of innovations, enabling it to navigate through the stomach and enter the small intestine. The RaniPill capsule goes through a transformation and injects the drug into the intestinal wall
- Rani Therapeutics completes first in human safety study of its robotic biologic pill and plans another one later this year
  - The Rani pill was found to be safe with no adverse events reported and bioavailability comparable to SC injection

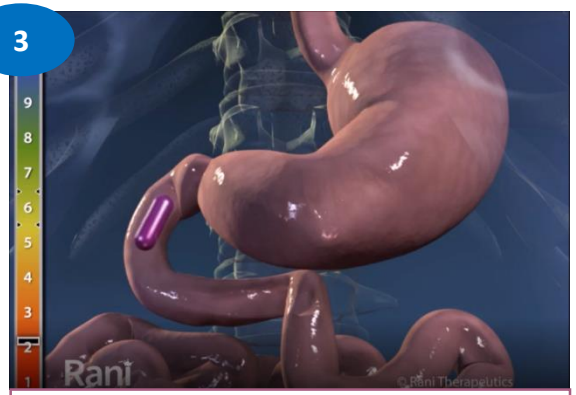
1

Capsule is taken through Oral Route

2

Special Enteric coating protects capsule from acidic environment in Stomach

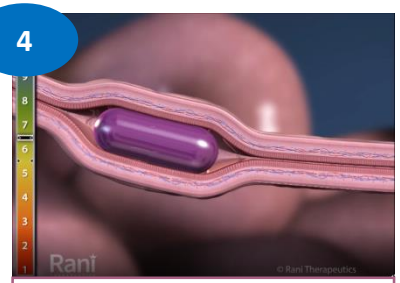
3



Capsule reaches Small intestine having high pH level

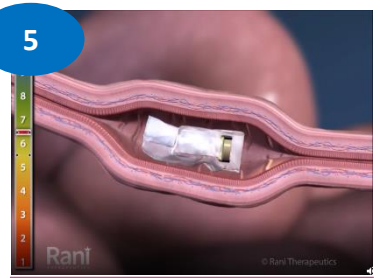
The highly vascularized intestinal wall allows the drug to be absorbed rapidly

4



Enteric coat starts dissolving

5

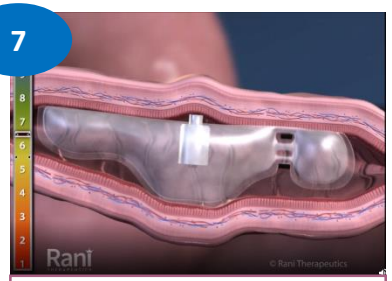


Enteric Coat dissolves completely

6

Intestinal fluid dissolves the valve

7

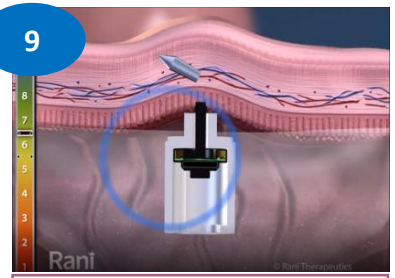


CO_2 generates that inflates the balloon

8

Pressure is created and injector is attached to Intestinal Wall

9

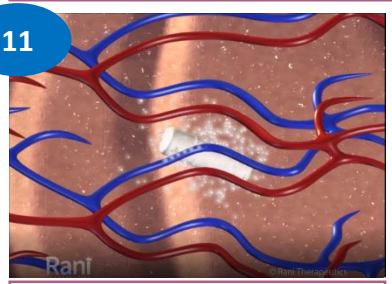


Drug is administered into intestinal wall

10

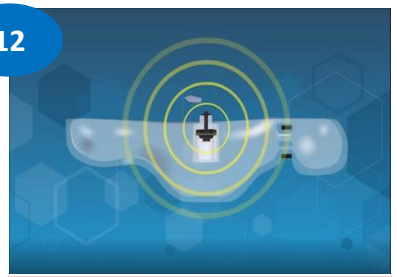
Balloon gets deflated and is passed out

11



Drug is quickly absorbed into highly vascularized intestinal wall

12

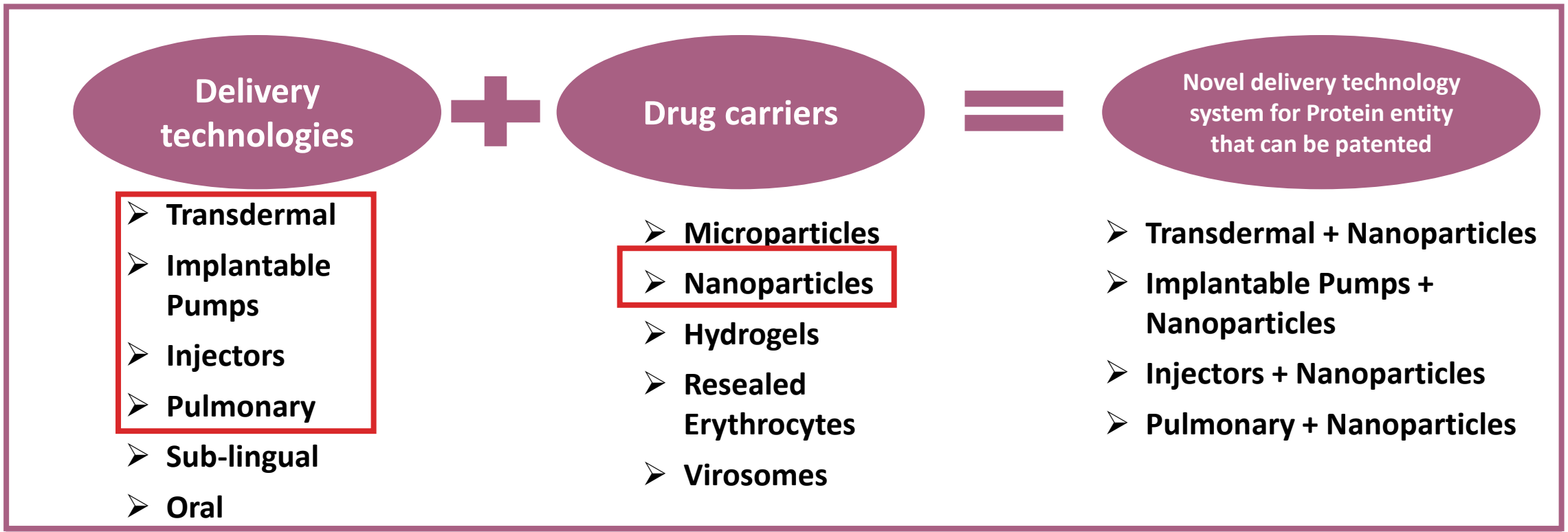


A tiny wireless sensor is incubated in capsule

13

A reminder message to take the capsule is sent

Conclusion: Delivery of protein entity using drug carriers along with a new mode of delivery might help it to obtain a patent



Consideration:

- Use of new delivery route alone may not give it a required edge over other cosyntropin, but **combining it with the novel drug carriers might help in obtaining a long-term patent protection** (due to increase in complexity of the technology)

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Thank You ☺