IRISYS

Concept to Commercial: A Clinical and Regulatory Outlook

BIOCOM CRO Committee Seminar

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Louis Scotti

IriSys:
From Preclinical to Commercial

Formulation Development

Analytical Methods Development

Regulatory and Drug Development

cGMP Clinical Supply Manufacturing

Commercial Manufacturing

Why is Commercialization Planning Important?

- Success is difficult to achieve and depends on early key decisions
- Product launches are complex and require preparation starting early in development
- Successful partnering requires more than good clinical data; value to diverse stakeholders must be convincingly demonstrated
- Successful commercialization planning is a key component of a strong and compelling BATNA*

*Best alternative to a negotiated agreement (HBS)

Commercialization Uncertainty is Multi-focal

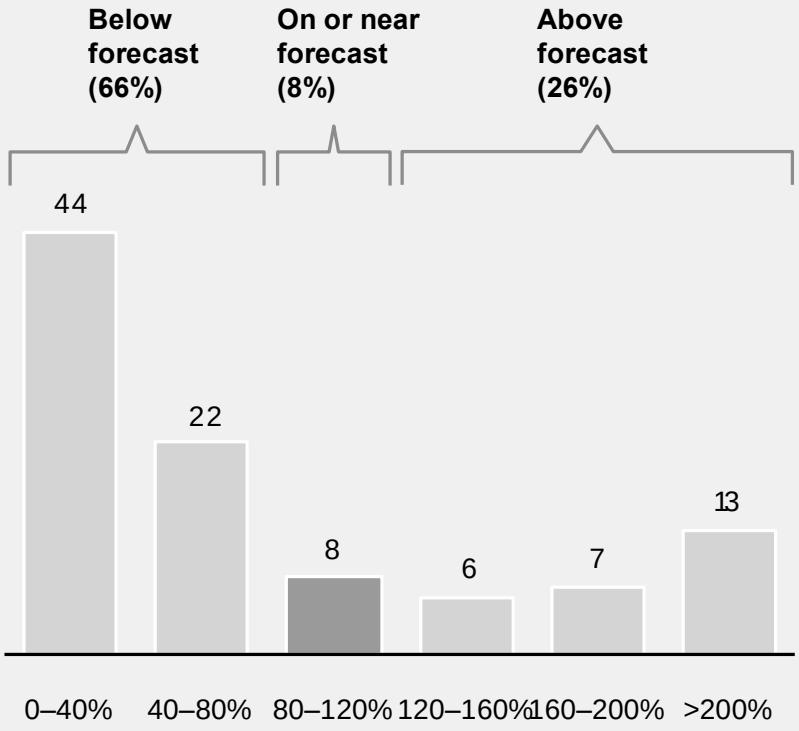
- Product uncertainty
  - Commercialization preparation must start long before clinical trials, labeling claims, pricing & reimbursement are finalized
- Market uncertainty
  - Shifting medical practices
  - Competitor response
  - Partnering interest
- Organizational uncertainty
  - Available resources
  - Financial health
  - Investor, equity market pressures

Source: McKinsey & Co 2013: Commercialization Excellence in the New Normal

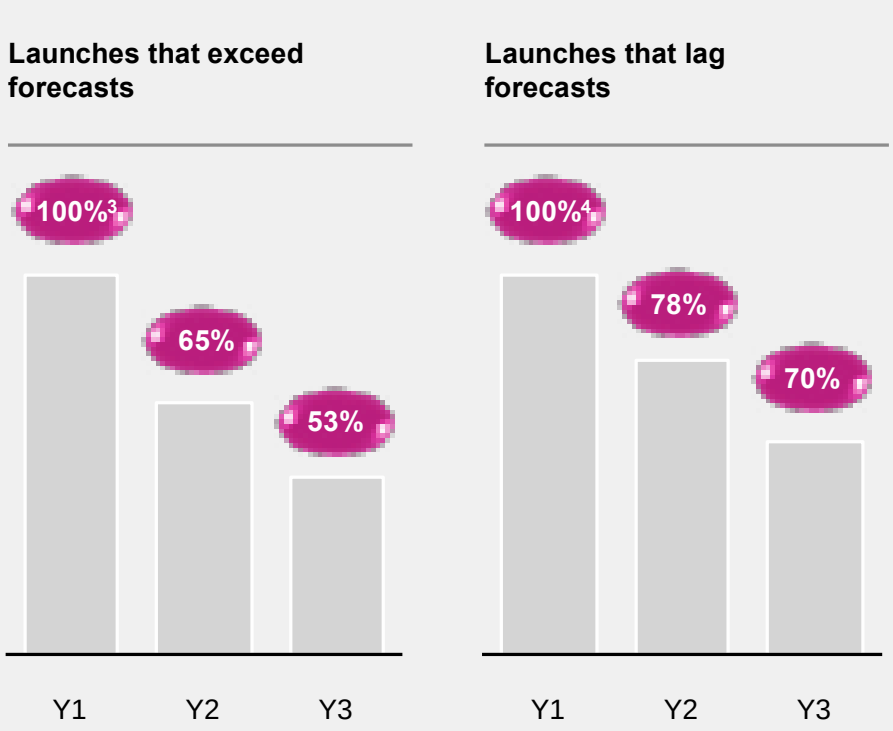
Below Forecast is the Norm

Exhibit 1: How launches perform against expectations

Ratio of actual sales at year of launch to forecast sales one year prior to launch[1]
% of launches



Launches that exceed or lag consensus forecasts in year 1 are likely to continue doing so[2]
% of launches

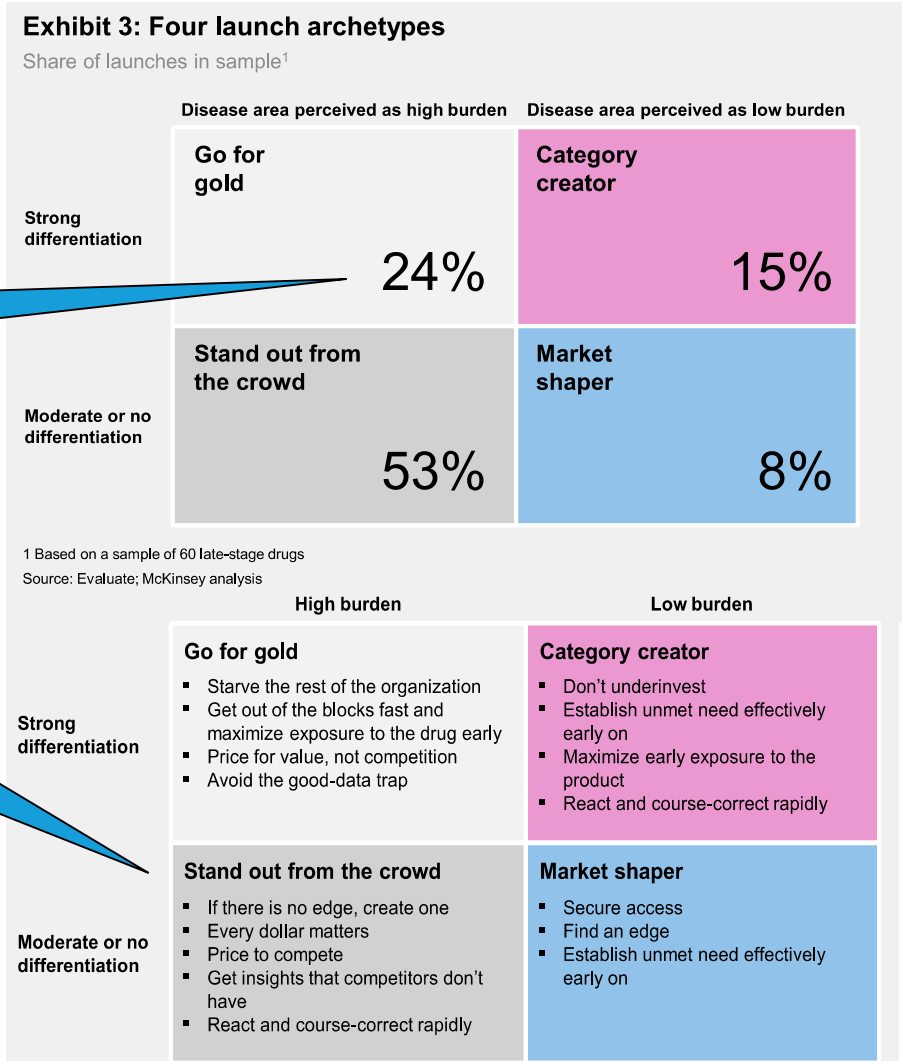


Source: McKinsey & Co 2013: Commercialization Excellence in the New Normal

Most Products Lack Differentiation

- Fewer than 1 out of 4 are strongly differentiated

- Products with clinically important differences require education
- Need to price competitively



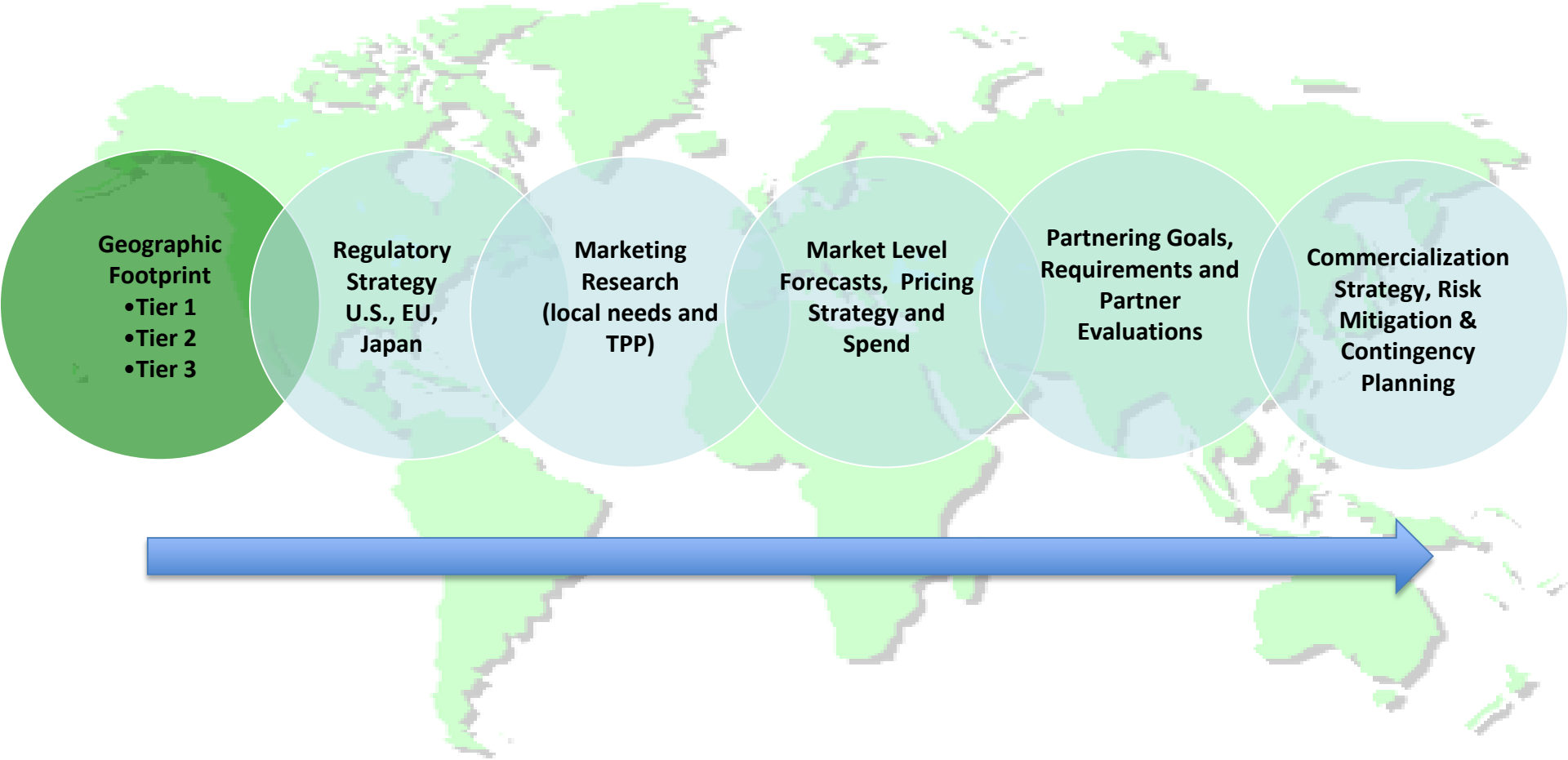
Source: McKinsey & Co 2013: Commercialization Excellence in the New Normal

Managing Commercialization Uncertainty

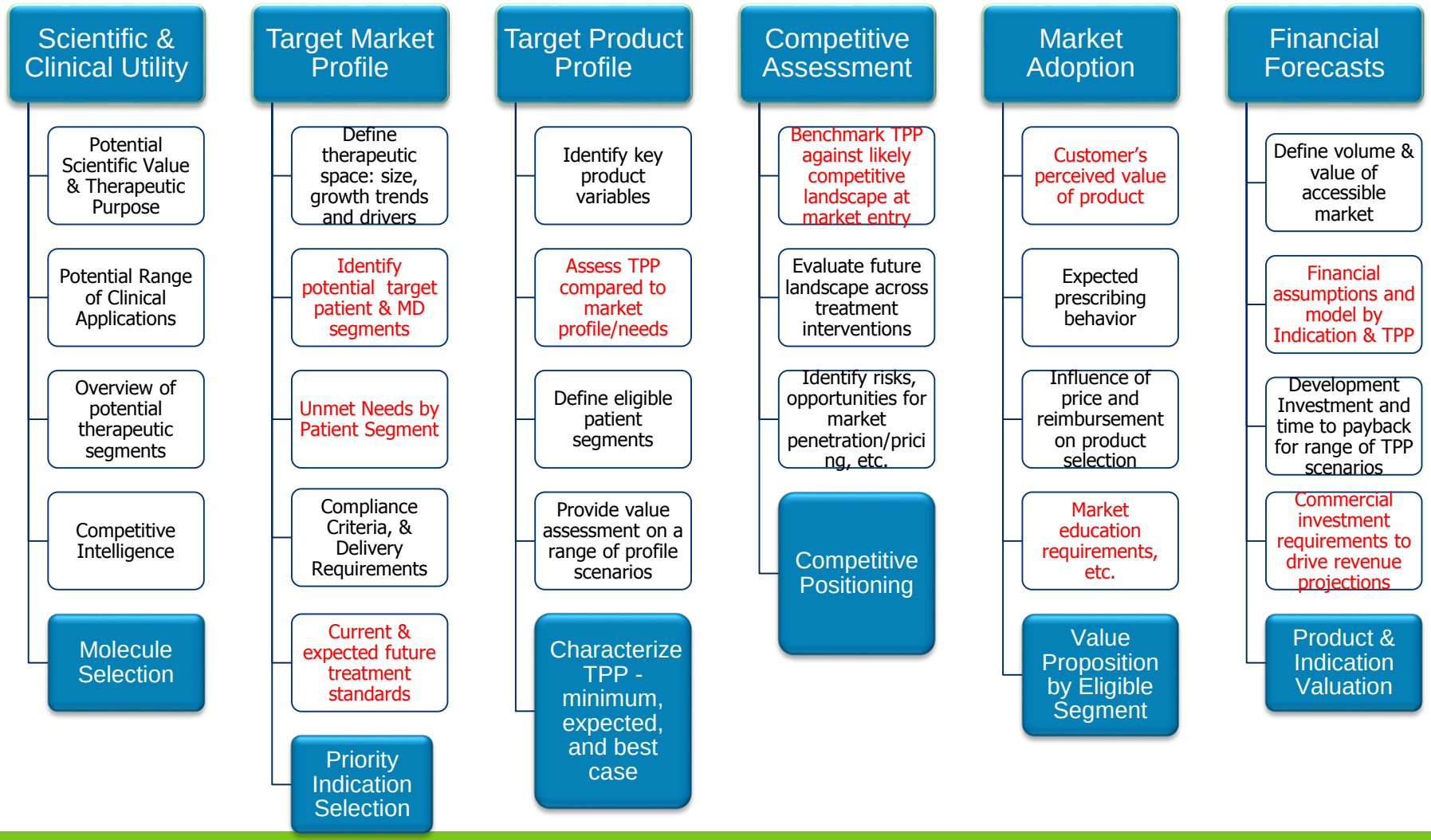
- Rarely do actual outcomes match one extreme possibility or another
  - Prepare for a reasonable range of likely outcomes
  - Don't ignore extremes
- Consider making at-risk investments to blunt or leverage resulting impact of important potential events
- Get a head start on dealing with likely outcomes
- Have a strategic Plan "B"

Source: McKinsey & Co 2013: Commercialization Excellence in the New Normal

Global Commercialization Strategy



Continuous Commercial Assessment



Target Product Profile

	Product X to manage "OFF"-episodes in Parkinson's patients
Product description	• Thin film sublingual formulation of apomorphine rescue therapy for intermittent "OFF"-episodes in Parkinson's patients • Similar efficacy to apomorphine injection with fewer total adverse events and less severe adverse events
Indication	• Treatment of acute and intermittent "OFF"-motor episodes in patients with Parkinson's disease
Mechanism of action	• Apomorphine is a dopamine agonist and adrenaline antagonist • Precise MOA in Parkinson's is unknown, but is believed to be due to stimulation of D_2-type receptors
Dosing and administration	• Sublingual film with available dose strengths equivalent to 2-6mg apomorphine injection • Tear/peel open single-dose package • One film applied during onset of "OFF"-motor symptoms • Can be used 1-5 times/day as needed for "OFF" episodes • Film dissolves in ~1 minute • Initial dose titration conducted in physician office to monitor for potential postural hypotension
Clinical efficacy	• Restoration of motor functions in ~5-15 minutes, with effects lasting 1 hour and greater • Mean change in baseline Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores of ~20-25 points versus ~0.1-7 points for placebo • Serum concentrations that are similar to the injection of apomorphine that result in rapid clinical efficacy
Safety and side effects	• Well tolerated by mouth • Patients provided with co-medication for 1-3 months to prevent emesis during adaptation • Adverse effects are transient (<1h) and include 20% yawning, 18% nausea, 15% dizziness, 11% somnolence, and 5-20% dyskinesia, comparable to apomorphine injection • Patients susceptible to hypotension (10%) and not eligible for apomorphine are identified during a physician monitored, in-clinic initiation procedure, comparable to apomorphine injection

Executive Summary

Disease

- Large patient population increasing at 8% CAGR
- 26 mil U.S. – 285 mil worldwide
- $116 bil direct U.S. medical costs in 2007

Market

- Metformin, sulfonylureas mainstays of oral therapies
- DPP4i, GLP1s, long-acting insulins dominate combo therapy
- $25 bil U.S. therapeutics market by 2015

Treatment Needs

- Risk-factor reduction
- Benefits in vulnerable patient populations
- Delay or prevent disease progression

XXX-001 TPP

- Non-systemic, new MOA may be attractive to FDA, physicians
- Potential positive effects on co-morbidities (e.g. lipids)
- Potential for weight reduction and delay of disease progression

XXX-001 TPP

Attribute	Minimal (acceptable for development)	Base (competitive w/DPP4i)	Optimal (≥$1 billion potential)
Indication	Improvement of glycemic control as evidenced by HbA1c reduction. Reduction in post-prandial glucose excursions.	In addition, reduction in post-prandial and/or long acting insulin.	In combination with DPP4i, improves CV risk factors, e.g. LDL, BMI.
Efficacy	Reduction in HbA1c of >0.7% monotherapy; 1 - 1.5% + DPP4i	Reduction in HbA1c of 0.7% to 0.8% monotherapy; 1.5 - 2% + DPP4i	Reduction in HbA1c exceeding 1% monotherapy; 1.5 - 2% + DPP4i
Safety	Non-absorbed (<1% bioavailability). No negative impact on GFR or GI transit time. No critical drug interactions, food interactions, or QT effect. Minimal risk of hypoglycemia (no worse than metformin or DPP4).	In addition: No increase in ALT. No decrease in fat-soluble vitamins.	In addition: No evidence of hypoglycemia.
Tolerability	Low (<5%) incidence of diarrhea, cramping, abdominal pain.		

XXX-001 TPP (cont.)

Attribute	Minimal (acceptable for development)	Base (competitive w/DPP4i)	Optimal (≥$1 billion potential)
Clinical Parameters	No worsening of comorbid conditions or any CV parameter. Mild, transient increases in triglycerides. Weight neutral.	Trend to increased HDL. No increase in triglycerides. Modest (<3%) weight loss.	Statistically significant increase in HDL; lowers LDL; ≥5% weight loss. Decreases triglycerides.
Dosing Method & Frequency	Oral tablet twice daily	Oral tablet once or twice daily	Oral tablet once daily
MOA	Increases fecal total bile acid concentration in the distal gut (ASBTi), thereby increasing production of GLP1 and PYY from intestinal L-cells. Non-systemic MOA.		
Pricing Potential	Comparable to Precose ($3-4/day)	Comparable to Januvia ($5-7/day)	Ranging from Byetta ($8/day) to Victoza (up to $12/day)
Reimbursement Potential	+	++	+++

Comparative Profiles

Attribute	XXX-001 (base TPP)	DPP4i	Long Acting GLP1	SGLT2i
Efficacy	↓ HbA1c 0.7 - 1% ↓ HbA1c 1.5 - 2% + DPP4i	↓HbA1c 0.7% mono ↓HbA1c 1.9% + DPP4i	↓HbA1c 0.8-1.1% mono ↓HbA1c 1-1.4% + DPP4i	Similar to DPP4i
Safety	↓ Hypoglycemia ✕ CV signals	↗Hypoglycemia (slight)	Immunogenicity, ↑pancreatitis, thyroid tumors in rodents	Bladder/breast cancer imbalance, fractures, renal function
Tolerability	↘ diarrhea, cramping	↗URI, headache (slight)	Headache, nausea, diarrhea, vomiting	UTI, genital infections
Dosing	1x – 2x daily	1x daily	1x weekly or monthly	1x daily
MOA	Non-systemic ASBTi	DPP4 inhibitor	GLP1 agonist	Sodium glucose transporter inhibitor
Clinical Parameters	↓LDL →Triglycerides ↘Weight	→Lipids →Weight neutral	↘LDL, trigs, ↗HDL ↘BP ↘Weight (-1.5-2.8 kg)	↘Hypoglycemia ↘Weight (-2-3 kg) ↘BP
Approval Timing	2016-2018	Approved (Januvia, Onglyza,	2012	2012 or later