EDISON

InMed Pharmaceuticals

Development update

Developing cannabinol (CBN)

Pharma & biotech

InMed has announced that the cannabinoid that is the basis for both its epidermolysis bullosa (EB) and glaucoma programs is cannabinol (CBN). This puts InMed in an attractive position (especially from an intellectual property perspective) as other medical cannabis programs are focused on either tetrahydrocannabinol (THC) and/or cannabidiol (CBD) for a variety of indications. Importantly, from a regulatory perspective, CBN is believed to have either slight or no psychoactivity, but it does have a number of beneficial effects including reducing inflammation and intraocular pressure (IOP).

Year end	Revenue (C$m)	PBT* (C$m)	EPS* (C$)	DPS (C$)	P/E (x)	Yield (%)
06/18	0.0	(5.3)	(0.04)	0.00	N/A	N/A
06/19	0.0	(9.1)	(0.05)	0.00	N/A	N/A
06/20e	0.0	(15.6)	(0.09)	0.00	N/A	N/A
06/21e	0.0	(17.3)	(0.10)	0.00	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

CBN: A minor cannabinoid with potential

CBN makes up substantially less than 1% of the cannabis plant and is a product of THC oxidation. Although related to THC, it is a relatively weak partial agonist of both cannabinoid receptors CB1 and CB2. In studies conducted so far on CBN, it has demonstrated little to no psychoactivity. However, there is evidence of efficacy across a number of indications.

Preclinical data presented at EB World Congress

The company recently presented data at the 2020 EB World Congress in London, which indicated that CBN has an effect on pain and inflammation that will likely be important in the treatment of EB. Also, CBN may significantly upregulate the keratin K_{15}, which may be able to compensate for a malfunctioning K_{14} and combine with K_5 to form the necessary adhesion between the epidermis and dermis. This could potentially lead to greater skin integrity and fewer blisters in EB simplex patients with K_{14} mutations.

CBN in glaucoma

In cats, CBN has previously been shown to significantly reduce IOP (the goal for a glaucoma therapy). The company believes it also has potential to have an impact on protecting the optic nerve. INM-088 has completed in vitro testing and InMed has initiated multiple formulation and pharmacology studies. These studies are expected to be completed in early 2020.

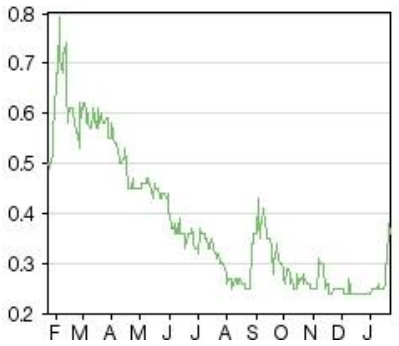
Valuation: C$259m or C$1.50 per basic share

We are maintaining our valuation of C$259m or C$1.50 per basic share (C$1.24 per diluted share). We will review our probabilities of success for INM-755 and INM-088 as the products progress. InMed had C$14.8m in cash and marketable securities at 30 September and we believe this provides a runway into FY21.

22 January 2020

Price	**C$0.36**
Market cap	**C$62m**
	C$0.75/US$
Net cash (C$m) at 30 September 2019	14.8
Shares in issue	172.3m
Free float	76.5%
Code	IN (TSX) IMLFF (OTC)
Primary exchange	TSX
Secondary exchange	OTC Markets

Share price performance



%	1m	3m	12m
Abs	47.9	26.8	(30.4)
Rel (local)	44.1	18.5	(39.2)
52-week high/low	C$0.79		C$0.23

Business description

InMed Pharmaceuticals is a Canada-based biopharmaceutical company focused on manufacturing and developing cannabinoids. Its biosynthesis platform may be able to produce cannabinoids for less cost and with improved purity compared to currently used methods. The company is also developing a proprietary pipeline, including INM-755 for epidermolysis bullosa, a serious, debilitating orphan indication.

Next events

755-101-HV trial enrolment completion	Q120

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Edison profile page

What is CBN?

First isolated in 1896, CBN makes up substantially less than 1% of the cannabis plant and is a product of THC oxidation (the amount of CBN in a plant increases the longer the plant is stored). CBN has a number of advantages as a development candidate. First, InMed is currently the only company with a CBN drug in the clinic. With first mover advantage, InMed should be positioned to gain broad intellectual property protection (this is especially true as CBN, while known for more than a century, was little studied). Second, in studies conducted so far on CBN, it has demonstrated little to no psychoactivity. Although related to THC, it is a relatively weak partial agonist of both cannabinoid receptors CB1 and CB2 (see Exhibit 1), although it may have efficacy through other mechanisms.[1]

Exhibit 1: Binding affinity ranges of select cannabinoids to CB1 and CB2 receptors

	CB1 Ki (nM)	CB2 Ki (nM)
THC	5.05–80.3	3.13–75.3
CBD	4,350–27,452	2,399–>10,000
CBN	120.2–1,130	100–301

Source: Pertwee et al., The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: D9-tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin. *British Journal of Pharmacology* (2008) 153, 199-215. Note: Higher levels indicate less binding affinity.

In one study in male volunteers, orally delivered CBN demonstrated no difference versus placebo with regard to psychoactivity, while THC showed a significant impact.[2] In another study in 21 male volunteers, testing THC, CBD and CBN, CBN rated as slightly more psychoactive than CBD, which is not considered to be psychoactive, and only at significantly higher doses than THC.[3] As a reminder, whatever psychoactivity CBN does have is not likely to be an issue for InMed as both INM-755 and INM-088 feature local administration, which minimizes systemic exposure. In preclinical testing, InMed saw no central nervous system (CNS) effects in local safety testing at 383 times the planned local dose. Systemic testing through subcutaneous injection of the drug in rats at 10,000 times the expected systemic exposure of the topical cream also indicated no CNS effects using 108 different CNS criteria.

Finally, and more importantly, there is evidence of efficacy across a plethora of indications. Key for the treatment of EB (a rare debilitating genetic dermatologic disorder characterized by skin fragility where just wearing normal clothing can lead to wound formation), CBN has been shown in a variety of published preclinical studies to have an effect on pain,[4] inflammation (due to the inhibition of the expression of cytokines)[5] and bacterial infection.[6] In addition, and recently presented at the 2020 EB World Congress in London, InMed has demonstrated in its own preclinical studies an effect on both pain and inflammation. In pain, InMed's research has demonstrated a positive impact in nerve

1 Zygmunt et al., Δ9-Tetrahydrocannabinol and Cannabinol Activate Capsaicin-Sensitive Sensory Nerves via a CB1 and CB2 Cannabinoid Receptor-Independent Mechanism. *Journal of Neuroscience*. 1 June 2002, 22 (11) 4720-4727

2 Karniol et al., Effects of D9-Tetrahydrocannabinol and Cannabinol in Man. *Pharmacology* 13: 502-512 (1975)

3 Perez-Reyes et al., A comparison of the pharmacological activity in man of intravenously administered delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. *Experientia*, 1973 Nov 15;29(11):1368-9

4 Zygmunt et al., Δ9-Tetrahydrocannabinol and Cannabinol Activate Capsaicin-Sensitive Sensory Nerves via a CB1 and CB2 Cannabinoid Receptor-Independent Mechanism. *Journal of Neuroscience*. 1 June 2002, 22 (11) 4720-4727

5 Jan et al., Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice. *Toxicology and Applied Pharmacology*, 188 (2003), 24–35.

6 Appendino et al., Antibacterial Cannabinoids from Cannabis sativa: A Structure−Activity Study. *Journal of Natural Products*, 2008 71(8), 1427–1430.

growth factor (NGF) induced pain models in rats. With regard to inflammation, CBN was tested on IL-8 and MMP-9, markers of inflammation suspected of having links with blister formation in EB simplex (both are upregulated in blisters) and in chronic cutaneous inflammation. Depending on dose, IL-8 was reduced by 35–54% and MMP-9 was reduced by 22–40%.

Also, based on InMed's preclinical research, CBN may significantly upregulate the keratin K_{15}. In two of three studies, K_{15} expression increased by 6–17 fold (in the one study that failed, there may have been an issue with the cells used). Higher K_{15} may be able to compensate for a malfunctioning K_{14} and combine with K_5 to form the necessary adhesion between the epidermis and dermis. This could potentially lead to greater skin integrity and fewer blisters in EB simplex patients with K_{14} mutations.

InMed has initiated its clinical trial program following Clinical Trial Application (CTA) approval in the Netherlands in December 2019. The Phase I program consists of two separate trials (see Exhibit 2). Trial 755-101-HV will enrol 22 healthy volunteers with normal, intact skin and evaluate the systemic and local safety, tolerability and pharmacokinetics (PK) of two dosage strengths of INM-755 cream. Trial 755-102-HV will have around eight healthy volunteers with small wounds to evaluate the local safety of the product. The small blister wounds will be created at the clinical site and will largely mimic the types of wounds typically seen in EB simplex patients. A Phase I/II in approximately 12–15 EB patients is expected to begin in early 2021 following additional IND/CTA filings globally. Note that all these trials will be double blind and vehicle controlled. Importantly, the safety studies can be used as the basis for a clinical trial program in other indications, as INM-755 may have applications in other dermatologic indications involving inflammation, pain and itch.

Exhibit 2: Expected clinical trial programme

Trial	Type of patients	Expected size	Treatment protocol	Purpose	Timing
Phase I (755-101-HV)	Adult healthy volunteers with normal, intact skin	22	14 days on intact skin; two dosage strengths	Systemic and local safety/PK	Initiated December 2019, complete enrolment by end of Q120.
Phase I (755-102-HV)	Adult healthy volunteers with small wounds	Around 8	Seven days on small wounds; two dosage strengths	Local safety	Initiate after 755-101-HV data are available. Enrolment expected to begin and complete in H220.
Phase I/II	EB patients (first adults, then children)	12–15	30 days on intact skin and possibly wounds; two dosage strengths	Systemic and local safety and efficacy	Initiate in Q121, following IND/CTA filings in additional countries globally.

Source: InMed Pharmaceuticals

CBN has also been shown to have efficacy in glaucoma. In cats, CBN has previously been shown to significantly reduce IOP (the goal for a glaucoma therapy) by around 27% after nine days.[7] If INM-088 is able to replicate this effect in humans, efficacy would be in the realm of current therapies (see Exhibit 3), which, while efficacious, have toxicity issues and low patient compliance (estimated at 41–78% of patients[8]).

7 Colasanti et al., Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. *Experimental Eye Research*, 1984 39(3), 251–259.

8 Denis et al., Adverse effects, adherence and cost-benefits in glaucoma treatment. *European Ophthalmic Review* 2011;5:116–122

Exhibit 3: Glaucoma treatment landscape

Drug class	Examples	Comments
Prostaglandins	Latanoprost (Xalatan, Pfizer), Lumigan (Allergan), Travatan Z (Alcon)	Reduce IOP by 28–33% (though may take three to five weeks to reach maximum IOP lowering) by relaxing muscles in the eye's interior structure to allow better outflow of fluids. Adverse events include redness and stinging, change of eye color, change in the pigment of the eye lashes or eyelid skin, lengthening and curling of the eyelashes, reactivation of herpes infection in the cornea, and uveitis.
Beta-blockers	Timoptic XE (Merck), Istalol (ISTA), Betoptic S (Alcon)	Reduce IOP by 20–30% by decreasing fluid production in the eye; typically additive to most IOP lowering agents. Exacerbate obstructive pulmonary diseases, slows heart rate and lowers blood pressure. Not recommended in patients with life-threatening depression. Betoptic tends to be the best tolerated drug in this class but at the expense of efficacy.
Alpha-adrenergic agonists	Iopidine (Alcon), Alphagan (Allergan)	Reduce IOP by 20–30% by decreasing rate of aqueous humor production (Iopidine and Alphagan) and increasing drainage (Alphagan). Adverse events include irregular heart rate, high blood pressure, fatigue and red, itchy or swollen eyes. Also, there is a high rate of allergy with Iopidine, which limits its use in chronic treatment.
Carbonic anhydrase inhibitors	Eyedrops: Trusopt (Merck) and Azopt (Alcon). Oral pills: Diamox (Sigma), Neptazane (Wyeth-Ayerst) and Daranide (Merck).	Eyedrops typically reduce IOP by 15–22% while oral versions reduce IOP by 25–35%. They work by decreasing the rate of aqueous humor production. Adverse events from eye drops include stinging, burning, eye discomfort and corneal edema. Adverse events from oral versions include tingling hands and feet, fatigue, decreased libido, depression, stomach upset, memory problems, frequent urination (from pill form).
Parasympathomimetics or cholinergic agents	Pilocarpine, carbachol	Reduce IOP by 15–25% by increasing the outflow of aqueous humor from the eye. Adverse events include constriction of the pupils, possible blurred or dim vision, near-sightedness, retinal detachment, intestinal cramps and bronchospasm.

Source: InMed, Canadian Ophthalmological Society

The company believes INM-088 also has potential to protect the optic nerve. INM-088 has completed in vitro testing and the company has initiated multiple formulation and pharmacology studies. These studies are expected to be completed in early 2020.

Valuation

We are maintaining our valuation of C$259m or C$1.50 per basic share (C$1.24 per diluted share), although we will review our probabilities of success for INM-755 and INM-088 as the products progress.

Exhibit 4: InMed valuation

Program	Stage	Probability of success	Launch year	Peak sales (C$m)	rNPV (C$m)
Biosynthesis (manufacturing)	Development	23%	2022	1,574	224
INM-755	Phase I	7.5%	2026	345	20
Total					244.4
Net cash and equivalents (as of 30 September) (C$m)					14.8
Total firm value (C$m)					**259.1**
Total basic shares (as of 30 September 2019, m)					172.3
Value per basic share (C$)					**1.50**
Options and warrants (as of September 2019, m)					37.4
Total diluted shares (as of September 2019, m)					209.7
Value per diluted share (C$)					**1.24**

Source: Edison Investment Research

Financials

InMed had C$14.8m in cash and marketable securities at 30 September and we believe this provides a runway into FY21. We continue to forecast the company will raise C$20m over the next two years to fund operations, which we model as illustrative long-term debt.

Exhibit 5: Financial summary

C$000s	2018	2019	2020e	2021e
Year end 30 June	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	0	0	0	0
Cost of Sales	0	0	0	0
Gross Profit	0	0	0	0
Research and development	(1,927)	(5,639)	(10,950)	(11,388)
Selling, general & administrative	(3,367)	(3,798)	(3,862)	(4,017)
EBITDA	(5,530)	(9,685)	(15,159)	(15,751)
Operating Profit (before amort. and except.)	(5,412)	(9,561)	(14,985)	(15,578)
Intangible Amortisation	0	0	0	0
Exceptionals/Other	(3,197)	(4,128)	(2,560)	(2,663)
Operating Profit	(8,609)	(13,689)	(17,546)	(18,240)
Net Interest	88	434	(626)	(1,708)
Other (change in fair value of warrants)	0	0	0	0
Profit Before Tax (norm)	(5,324)	(9,127)	(15,612)	(17,286)
Profit Before Tax (IFRS)	(8,521)	(13,255)	(18,172)	(19,948)
Tax	0	0	0	0
Deferred tax	0	0	0	0
Profit After Tax (norm)	(5,324)	(9,127)	(15,612)	(17,286)
Profit After Tax (IFRS)	(8,521)	(13,255)	(18,172)	(19,948)
Average Number of Shares Outstanding (m)	142.5	171.3	174.9	181.9
EPS - normalised (c)	(3.74)	(5.33)	(8.93)	(9.50)
EPS - IFRS (C$)	(0.06)	(0.08)	(0.10)	(0.11)
Dividend per share (c)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	1,329	1,241	1,807	1,242
Intangible Assets	1,274	1,185	1,160	1,160
Tangible Assets	56	56	647	83
Other	0	0	0	0
Current Assets	26,734	18,548	12,763	5,547
Stocks	0	0	0	0
Debtors	0	0	0	0
Cash	26,477	18,039	12,474	5,258
Other	257	509	288	288
Current Liabilities	(938)	(1,563)	(1,462)	(1,462)
Creditors	(938)	(1,563)	(1,462)	(1,462)
Short term borrowings	0	0	0	0
Long Term Liabilities	0	0	(10,410)	(20,410)
Long term borrowings	0	0	(10,000)	(20,000)
Other long term liabilities	0	0	(410)	(410)
Net Assets	27,125	18,226	2,698	(15,083)
CASH FLOW				
Operating Cash Flow	(4,672)	(8,769)	(15,284)	(17,024)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(56)	(35)	(174)	(192)
Acquisitions/disposals	0	0	0	0
Financing	24,483	273	0	0
Dividends	0	0	0	0
Other	0	0	1	0
Net Cash Flow	19,756	(8,532)	(15,458)	(17,216)
Opening net debt/(cash)	(6,708)	(26,477)	(18,039)	(2,474)
HP finance leases initiated	0	0	0	0
Exchange rate movements	0	0	0	0
Other	14	94	(107)	0
Closing net debt/(cash)	(26,477)	(18,039)	(2,474)	14,742

Source: InMed Pharmaceuticals accounts, Edison Investment Research

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