EDISON

Intec Pharma

Outlook

Ongoing AP clinical trials

Pharma & biotech

Intec Pharma's clinical programmes to validate the utility of its unique drug delivery platform, the accordion pill (AP), are ongoing. The company announced with its Q317 report that patient enrolment for the Phase III AP-CDLD (carbidopa and levodopa) in Parkinson's has been increased to 420 patients (from 328). We now expect full enrolment in Q318. Additionally, Intec is redesigning AP-CBD/THC (cannabidiol and tetrahydrocannabinol) for a second Phase I trial and the indication is not yet specified.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/15	0.0	(7.2)	(0.92)	0.0	N/A	N/A
12/16	0.0	(13.4)	(1.17)	0.0	N/A	N/A
12/17e	0.0	(23.2)	(0.88)	0.0	N/A	N/A
12/18e	0.0	(18.2)	(0.65)	0.0	N/A	N/A

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

AP-CDLD enrolment upsized and trial delayed

Intec has announced that it is expanding target enrolment for the Phase III AP-CDLD trial to 420 patients (after downsizing enrolment to 328 from 460 patients), due to higher than expected dropout rates associated with endoscopy procedures prior to randomization and open-label Sinemet titration that comes before AP exposure. The company now expects completion of enrolment in Q318 (previously Q417). Provided that patients are followed for 26 weeks, we expect top-line data in mid-2019.

Redesigning AP-CBD/THC and a new Phase I

Although AP-CBD/THC improved exposure of CBD by 290% to 330% and THC by 25% to 50%, and increased time at peak concentration (2-3x longer) compared to Sativex without raising any safety or tolerability concerns in the Phase I trial, Intec recently stated that it is in the process of redesigning the AP for CBD/THC to improve efficacy and has plans to initiate an additional Phase I trial; however, timing has not been disclosed. The company has not yet specified the target indication (either low back pain or fibromyalgia). Due to these factors, we do not include the AP-CBD/THC programme in our valuation at this time.

Valuation: NIS619m ($176m) or NIS23.85/share ($6.79)

We have decreased our valuation to NIS619m ($176m) or NIS23.85 ($6.79) per basic share, from NIS737m ($205m) or NIS28.39 ($7.91) per basic share. This is driven by the de-prioritization of the AP-ZP (zaleplon) insomnia programme, higher development costs for the AP-CDLD programme due to enrolment expansion delaying complete enrolment to Q318 (previously Q417) and launch year to 2020 (previously 2019), and lower net cash. This is partially mitigated by rolling forward our NPVs. We expect to update our valuation to reflect data from the Phase III AP-CDLD trial and progression of the cannabinoid programme. We do not believe Intec will require any more cash to break even, which we estimate will be in 2020.

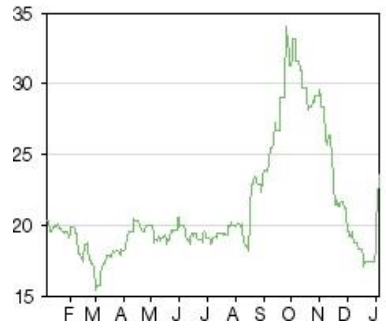
7 January 2018

Price*	**NIS23.50**
Market cap	**NIS613m**

*Priced at 4 January 2018

	NIS3.51/$
Net cash ($m) at 30 September 2017	64.7
Shares in issue	26.1m
Free float	78%
Code	NTEC
Primary exchange	TASE
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	22.3	(29.2)	16.7
Rel (local)	17.2	(33.6)	7.9
52-week high/low	NIS34.1	NIS15.4	

Business description

Intec Pharma is a drug delivery company that has developed the accordion pill, a novel gastroretentive controlled release formulation. The company is currently using this technology to develop AP-CDLD for Parkinson's (in Phase III) and AP-CBD/THC (in Phase I for pain indications).

Next events

AP-CBD/THC indication announced	H118
AP-CDLD enrolment complete	Q318

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Edison profile page

Investment summary

Company description: A unique drug delivery platform

Intec Pharma is a drug delivery company, which went public via an IPO on TASE in 2010 and NASDAQ in 2015. The company's core technology is the accordion pill (AP), a controlled release drug delivery device in the form of layered membranes that are delivered in a normal capsule pill. The device expands in the stomach, leading to retention for up to 12 hours. This process is ideal for drugs that must be delivered to the upper digestive tract and drugs that dissolve poorly. Intec Pharma has developed AP-CDLD for Parkinson's disease (in Phase III). The company completed a Phase I trial of cannabinoids for pain (and potentially other indications) in Q317. There is also an undisclosed product in Phase I for the prevention of NSAID induced ulcers of the stomach, duodenum and bowel. It has a development agreement with Biogen to develop an AP formulation of one of Biogen's approved drugs.

Valuation: NIS619m ($176m) or NIS23.85 ($6.79) per share

We have decreased our valuation to NIS619m ($176m) or NIS23.85 ($6.79) per basic share from NIS737m ($205m) or NIS28.39 ($7.91) per basic share. This reduction is largely attributed to the removal of the AP-ZP (zaleplon) programme for the treatment of insomnia from our valuation as the company is currently focusing its resources towards the AP-CDLD and AP-CBD/THC development programmes. The change is also driven by the increase in development costs associated with the AP-CDLD programme due to enrolment expansion, which delays complete enrolment to Q318 and therefore launch year to 2020, and lower net cash. This is partially mitigated by increasing our US price growth rate assumption from 2% to 4% based on current pharmaceutical industry pricing power specifically within Parkinson's Disease and rolling forward our NPVs. We expect to update our valuation to reflect data from the Phase III AP-CDLD trial, progression of the cannabinoid programme, and with more information on the two undisclosed programmes.

Financials: Increased R&D spending

We have increased our expected R&D spending for 2017 to $19.4m from $17.1m due to enrolment expansion for the AP-CDLD Phase III trial to 420 patients (from 328 patients). The company ended the period with $65m in cash and equivalents. We believe that this is sufficient capital for the company to break even, which we estimate will be in 2020.

Sensitivities: Commercial risks

Intec's development risks are largely concentrated on whether the AP technology can provide a definitive benefit over other controlled release (CR) formulations. The company has MRI evidence that APs are effectively retained in the stomach, but the question remains as to how this translates into a benefit for any given compound. The advantages of the formulation are most well-established for AP-CDLD, which demonstrated superior results to existing CR carbidopa/levodopa in Phase II. Intec faces significant commercial risks, because Parkinson's and insomnia are two markets dominated by generics, with very large numbers of treatment options. In the case of Parkinson's, there are multiple programmes aimed at the same treatment axis as AP-CDLD and with regard to insomnia, prescription hypnotics are half the total number of prescriptions for the disease, but are dominated by OTC treatments. Financial risks for the company are limited, especially compared to other companies at this stage. The FDA confirmed 505(b)2 pathway eligibility for AP-CDLD, which limits development costs.

Company description: A better formulation option

Intec is an Israeli specialty pharmaceutical company developing new formulations of existing drugs using its proprietary accordion pill (AP) technology. Intec has five development programmes based on the AP technology. The most advanced programme is AP-CDLD, an AP formulation of the well-established Parkinson's drugs carbidopa and levodopa, which have proved difficult to formulate effectively in an extended release pill for an array of reasons. The programme in is Phase III. Intec has also completed a Phase I trial of AP-CBD/THC, an AP with two primary cannabinoids in Cannabis sativa, cannabidiol (CBD) and tetrahydrocannabinol (THC) for treatment of "various indications, including low back pain and fibromyalgia", although the company has made no commitments to study either. The company is currently redesigning AP-CBD/THC to improve performance and has stated that it plans to initiate a second Phase I study in the near future. Intec remains Phase III ready with AP-ZP, an AP with zaleplon for the treatment of insomnia; however the company has stated that it is not actively pursuing a partner to continue with development and potential commercialization at this time and is instead focusing its efforts on the AP-CDLD and AP-CBD/THC programmes. A fourth clinical programme is investigating a product to reduce the risk of NSAID induced ulcers in the stomach, duodenum and small bowel. Intestinal ulcers, unlike peptic ulcers, are poorly controlled with proton pump inhibitors. The details of this programme are undisclosed. Also undisclosed are the details of a preclinical partnership with Biogen to develop an AP formulation of one of Biogen's approved medications. Although not a current focus for the company, Intec is entitled to $8m upfront, $39m in milestones and a low single-digit royalty on sales up to $100m, should Biogen exercise the option.

Exhibit 1: Intec pipeline

Programme	Stage	Indication	Molecule(s)
AP-CDLD	Phase III	Parkinson's	Carbidopa and levodopa
AP-CBD/THC	Phase I	Multiple including pain	Cannabinoids
AP-ZP	Phase III ready	Insomnia	Zaleplon
Undisclosed drug	Phase I	Prevention of NSAID induced gastroduodenal and small bowel ulcers	Undisclosed
Biogen partnership	Preclinical	Undisclosed	Approved Biogen drug

Source: Intec Pharma

AP drug delivery

Intec's key innovation is the development of the AP drug delivery platform. The AP technology uses a typical gel-cap pill, which dissolves in the stomach to release a folded, two-dimensional, composite film impregnated with the drug of interest. The AP expands on exposure to the gastric medium to 3.5cm in length, and is retained in the stomach while drug is released.

Exhibit 2: AP drug release profile

Key feature	Notes
Inner drug matrix	Polymer matrix impregnated with the drug of interest and designed to dissolve when exposed to the gastric medium.
Outer membranes	"Envelope" that surrounds the inner matrix. These membranes are hydrophilic and swell on exposure to the gastric medium, but are resistant to degradation in the stomach. The swelling of these membranes exposes the inner drug layer to the gastric juices allowing it to dissolve, while retaining the physical profile of the AP. This layer fully dissolves in the lower digestive tract.
Optional immediate release layer	Layer of drug in a matrix or film applied to the outside of the AP, designed to dissolve immediately after the drug reaches the stomach.

Source: Intec Pharma

Intec is currently investigating the formulation for a series of controlled release (CR) applications because of a set of distinct advantages the AP has over other existing CR formulations. One of the central characteristics of the AP is that its expansion in the stomach leads to unprecedented gastric retention times (eight to 12 hours), as measured through MRI imaging. The gastric retention is

driven by the device's physical size, its two-dimensional profile and its rigidity, which discourage passage through the pylorus. Unlike other CR formulations that release drug continuously though their passage of the digestive tract, the AP isolates this dissolution to the stomach and the drug is absorbed primarily in the duodenum and proximal small intestine, which can be important for drugs that have local activity or specific absorption in these regions. This provides a uniform absorption profile and can potentially improve plasma levels by prolonging the absorption phase. Moreover, the solubilisation of the drug is aided by the high concentration of bile acids. This consideration is important as an increasing number of new drugs are of low solubility, up to 60% by some measures.[1]

AP-CDLD: The lead development programme

Intec's lead product is an AP co-formulation of carbidopa and levodopa (AP-CDLD) for the treatment of Parkinson's disease. Parkinson's disease is a neurodegenerative disease in which the dopamine secreting (dopaminergic) neurons in the brain are lost, leading to severe motor defects and cognitive impairment. Approximately one million people in the US have Parkinson's and it affects 1.75% of people over 60.[2,3]

Carbidopa and levodopa is the most widely used treatment for Parkinson's worldwide. Levodopa, (L-DOPA) is a precursor to dopamine which, unlike the neurotransmitter, is able to cross the blood-brain barrier. High doses of this molecule can increase dopamine concentrations in the brain and alleviate some of the symptoms associated with the loss of dopaminergic neurons. However, the molecule is also quickly converted into dopamine outside the brain, which is associated with gastrointestinal and other side effects, and significantly reduces the concentration of drug available to the brain. This effect is circumvented by the co-administration of carbidopa, which inhibits this conversion in peripheral tissue. Despite this, however, there are significant limitations to the administration of levodopa that limit its utility. Even with the co-administration of carbidopa, levodopa is still metabolised quickly with a half-life of 1.5 hours, leading to a pharmacokinetic profile with high peaks and deep valleys throughout the day. The valleys are associated with the motor defects typical of the disease, also known as being "off", and the peaks can cause dyskinesia that interferes with normal function, leaving a fraction of a patient's day where s/he is well treated. As the disease progresses, the therapeutic window for the drug gets smaller, leaving limited time in which the patient is in an "on" state without troublesome dyskinesia.

Intec has developed AP-CDLD to address the issues of existing formulations. The properties of the AP lend themselves well to the delivery of these drugs, and the drug is formulated with levodopa in the controlled release inner layer and carbidopa in an immediate release layer. Levodopa is only absorbed in the upper gastrointestinal (GI) tract because it requires an active transporter to ferry it across the intestinal wall that is only present in this location. Moreover, the controlled release properties of AP-CDLD could potentially improve the pharmacokinetic profile of the drug, reducing peaks and valleys and therefore reducing off time and dyskinesia.

Phase II results and Phase III enrolment

AP-CDLD for the treatment of moderate to severe Parkinson's in a Phase II study demonstrated superior results to existing CR carbidopa/levodopa. The trial consisted of multiple sub-studies designed to examine the dosing, pharmacokinetics (PK) and efficacy of the formulation.

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1 Ku, MS (2008) Use of the Biopharmaceutical Classification System in Early Drug Development. *AAPS J.* 10, 208-212.

2 Parkinson's Disease Foundation.

3 Cleveland Clinic.

In the PK portion of the trial, eight patients were stabilised on either AP-CDLD with 50mg carbidopa and 375mg levodopa twice a day, or an equivalent amount of both drugs in an immediate release formulation four times a day, and the daily time course of levodopa blood concentration was measured. The study found that the AP formulation of these chemicals substantially reduces the "peak and valley" profile typical of levodopa administration. Patients were able to maintain a relatively constant blood concentration of levodopa, with only a threefold change in the ratio of maximum and minimum exposure. Also interesting was discovering that patients on AP-CDLD woke up with 500ng/mL of levodopa in their system, meaning that the kinetic profile of the drug was able to maintain some exposure throughout the night and into the morning following the day's last dose (12 hours before waking). Although it is not likely that this low concentration supressed symptoms, the result suggests that AP-CDLD could potentially be effective as an overnight drug. Morning off states are typically the most severe of the day for patients with Parkinson's and there are currently no options for oral carbidopa and levodopa that last through the night.

In the efficacy portion of the Phase II trial, two arms had a crossover design structured to investigate AP-CDLD at two different doses compared to the same patients on their optimised current carbidopa/levodopa-based treatment. The three endpoints were the difference in off time, on time with troublesome dyskinesia, and the number of additional levodopa doses needed. Of the patients that were comparable after three weeks in the study, 16 received AP-CDLD with 50mg carbidopa and 375mg levodopa (50/375) twice a day and 18 received AP-CDLD with 50mg carbidopa and 500mg levodopa twice a day (Exhibit 3).

Exhibit 3: AP-CDLD Phase II efficacy results

	AP-CDLD 50/375mg (n=16)			AP-CDLD 50/500mg (n=18)			Rytary (n=393)			Comtan (n=205)		
	Current treatment	AP-CDLD	p	Current treatment	AP-CDLD	p	CDLD	Rytary	p	Placebo +CDLD	Comtan + CDLD	p
Off time (h)	4.3	2.4	<0.0001	5.1	2.8	<0.0001	4.88	3.87	<0.0001	5.3	4.2	<0.001
On time with troublesome dyskinesia (h)	0.7	0.6	N/S	1.2	0.7	0.002	0.45	0.52	N/S		increased[4]	0.002
Number of daily LD administrations	6.3	3.5	<0.0001	5.3	4	<0.0001	5.1	3.6	<0.0001	6.2	5.8	<0.001

Source: Intec Pharma, Rytary approval review documents, Comtan approval review documents, Parkinson's Study Group. Note: Rytary and Comtan data reflect patients stabilised on different dosing regimens. CD = carbidopa, LD = levodopa, N/S = not significant.

The study found that AP-CDLD was more effective at reducing off time at both dosing regimens, and the result was statistically significant by a wide margin (p<0.0001). The total mean reduction in off time of 1.9 hours per day was larger for AP-CDLD than has been previously observed for either Rytary or Comtan (1.0 hours and 1.1 hours, respectively). Moreover, the mean amount of on time with troublesome dyskinesia was reduced at the higher dose by 0.5 hours per day. It is understandable that this effect was only seen at the higher dose because patients with more severe Parkinson's disease on higher doses of levodopa tend to experience this side effect with higher frequency. This result was not seen in the Phase III studies of Rytary, although it should be noted that baseline troublesome dyskinesia was substantially lower (0.35-0.37 hours per day) than seen in patients in the AP-CDLD trial. Studies of Comtan have shown that it increases the rate of dyskinesia (53% of patients compared to 32% for placebo, p=0.002).[4] It should be noted that in the Rytary and Comtan trials, patients were optimised to different dosing regimens, and the data reflect an average of these optimised treatments.

The third measure of efficacy tracked in the study was the number of daily support doses of levodopa needed as part of the patient's current treatment or on top of AP-CDLD. The number of additional pills was reduced by 2.8 per day on the lower AP-CDLD dose, and 1.3 on the higher dose. The reduction is not particularly surprising considering that AP-CDLD is providing a significant amount of levodopa and therefore reducing the total needed by a patient via other means throughout the day. However, this does give a measure of the pill burden for patients on this

[4] Parkinson's Study Group (1997) Entacapone Improves Motor Fluctuations in Levodopa-Treated Parkinson's Disease Patients. *Ann. Neurol.* 42, 747-755.

treatment whereas pill burden can be significant for Parkinson's patients, considering the number of overlapping treatment regimens these patients require. This finding indicates that the lower dose AP-CDLD may reduce the overall pill burden (two pills of AP-CDLD but 2.8 fewer other pills) and, although patients requiring the higher dose may have an increased pill burden, it is small (approximately one extra pill) considering the benefit to off time and dyskinesia.

The FDA confirmed AP-CDLD eligibility for 505(b)2 pathway to approval, which enables a marketing application after just one Phase III trial. The study enrolled its first patient in April 2016 and consists of a head-to-head comparison between AP-CDLD and the immediate release carbidopa/levodopa drug Sinemet. The trial is randomized and double blind and will examine two dosage strengths of AP-CDLD (50mg carbidopa with either 400mg or 500mg levodopa) at two to three times daily. Prior to randomization, patients will be stabilised on both Sinemet and AP-CDLD to determine the correct dosing regimen, and will then receive one of the drugs concurrently with a dummy version of the other (to prevent unblinding due to different dosing frequencies). Patients will be able to take two to three pills per day of AP-CDLD at two different doses (50/400mg or 50/500mg of carbidopa/levodopa). An important difference from the Phase II is that patients on the AP-CDLD arm will not be supplementing with immediate release levodopa if needed, which may increase off time, although this will be mitigated by the ability to take up to three APs per day if needed. The primary endpoint of the trial will be the reduction in number of off hours, as reported by a patient diary, but other efficacy measures such as the change in troublesome dyskinesia and global assessments such as the Unified Parkinson's Disease Rating scale (UPDRS) will be made.

The company announced on its Q317 call that it is upsizing target enrolment for the Phase III study to 420 patients, after previously reducing enrolment to 328 patients (from 460 patients announced in July). The company stated that the increase is due to higher than expected dropout rates associated with endoscopy procedures prior to randomization and open-label Sinemet titration that comes before AP exposure. Complete enrolment has been delayed to Q318 (from Q417) due to the increased patient target. Provided that patients are followed for 26 weeks, we expect top-line data in mid-2019. Following completion of the trial protocol, patients will be entered into an open label extension, data from which may provide early insights into efficacy.

Market and competitive environment

Parkinson's disease treatment is multifaceted and typically requires several simultaneous pharmacological interventions on top of levodopa treatment to achieve optimal control. Treatment includes dopamine agonists, glutamate antagonists, monoamine oxidase inhibitors and other classes of drugs in addition to levodopa and drugs used in conjunction with it. Because of this, there are an exceptionally large number of drugs that are marketed or in development for this indication, measured in the hundreds. However, there are substantially fewer programmes directly addressing the levodopa treatment axis that might affect the potential market for AP-CDLD.

There are approximately 300k total prescriptions for carbidopa/levodopa per month in the US[5] and the market is dominated by generics, which constitute 97% of these prescriptions. There are two branded controlled release formulations of carbidopa and levodopa that are commercially available: Sinemet CR and Rytary (Numient in Europe). Sinemet CR did not compete well against generic immediate release carbidopa/levodopa because the pill is both slow to relieve off states and had low systemic bioavailability, requiring increased dosing over immediate release products. Generic equivalents to Sinemet currently have 14% market share. Rytary, which was approved in 2015, was designed to address some of the limitations of Sinemet CR, and incorporates an immediate release component to provide instantaneous relief from off states. Sales of Rytary are not explicitly stated by sponsor Impax Laboratories, but Symphony Health reports US sales of $76.9m for FY16 and approximately 4% market share in 2017.

[5] Symphony Health

A prominent programme that has addressed the levodopa delivery problem is Duopa (AbbVie, Duodopa ex-US), which is a gel formulation of carbidopa and levodopa that is delivered directly to the duodenum via an implanted pump. This device continuously infuses the drugs and is effective at reducing off states (63% reduction, twice the effect of immediate release pills) and dyskinesia (86% more on time without dyskinesia compared to immediate release pills), but requires major surgery. We therefore expect it to be limited to only the most poorly controlled patients. The product was approved in the US in early 2015, but has been approved in Europe since 2004. In 2016 the product sold $293m, with 87% of sales in Europe.

We consider a number of programmes to be direct competitors to drugs like AP-CDLD and other attempts to achieve sustained levodopa serum levels (Exhibit 4). The vast majority of these programmes in development have remained relatively stagnant over the last year. Albeit this is quite common in the pharmaceutical industry, the apparent standstill potentially suggests that Parkinson's is in fact a complex indication to treat.

Exhibit 4: Levodopa treatment axis programmes

Status	Name	Molecule(s)	Company	Notes
Approved	Comtan	entacapone	Novartis	First approved COMT inhibitor
Approved	Duopa	carbidopa; levodopa	AbbVie	Gel formulation delivered directly to duodenum via a pump
Approved	Rytary	carbidopa; levodopa	IMPAX Laboratories	Immediate and controlled release formulation
Approved	Sinemet CR	carbidopa; levodopa	Bristol-Myers Squibb	First approved controlled release CD LD formulation
Approved	Stalevo	carbidopa; entacapone; levodopa	Novartis	CD LD COMT combo pill, immediate release
Filed	Ongentys	opicapone	BIAL	"Third generation" COMT inhibitor
Phase III	LECIGon	carbidopa; entacapone; levodopa	LobSor Pharmaceuticals	Gel formulation deliver directly to duodenum via a pump
Phase III	CVT-301	levodopa	Acorda Therapeutics	Inhalable levodopa
Phase II	DM-1992	carbidopa; levodopa	Depomed	Gastroretentive immediate release/extended release co-formulation. Development suspended
Phase II	DopaFuse	carbidopa; levodopa	SynAgile	Drug delivered via a continuous oral pump
Phase II	IPX203	carbidopa; levodopa	IMPAX Laboratories	Follow on for Rytary. Fast onset followed by extended release
Phase II	ND0612H	carbidopa; levodopa	NeuroDerm	Liquid formulation delivered via a dermal pump
Phase II	XP21279	levodopa prodrug	XenoPort	Sustained release levodopa prodrug designed to improve absorption. Development halted pending a partnership
Preclinical	ATT-LD	levodopa prodrug	Aposense	Long-acting levodopa prodrug
Preclinical	CERC-406	-	Cerecor	COMT inhibitor that passes the blood brain barrier

Source: EvaluatePharma, company documents

AP pipeline progress

Intec has two additional, disclosed AP-based programmes: AP-CBD/THC, a co-formulation of two primary cannabinoids in Cannabis sativa, cannabidiol (CBD) and tetrahydrocannabinol (THC) potentially for the treatment of low back pain or fibromyalgia in Phase I, and AP-ZP, a formulation of zaleplon for the treatment of insomnia that is Phase III ready.

AP-CBD/THC: Another Phase I

Intec is developing a cannabidiol/tetrahydrocannabinol accordion pill as there are several aspects of cannabinoid pharmacology that could potentially be improved by the AP formulation. Cannabinoids have a low oral bioavailability measured at an average of 6% for THC[6] and CBD,[7]

[6] Ohlsson A, et al (1980) Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin. Pharmacol. Ther.* 28, 409-16.

[7] Agurell S, et al. (1981). Interaction of THC with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. Experientia 37, 1090–2.

although with high levels of variability between individuals and doses even when administered under similar conditions. THC and CBD are very oily molecules that dissolve poorly in the aqueous gastric medium. The dissolution and absorption of the drug is aided in the gut by bile acids. The AP device is specifically designed to maximize the exposure of drugs to bile acids secreted in the upper gastrointestinal tract, and an AP-CBD/THC formulation may significantly improve the drug's oral profile.

The company completed the AP-CBD/THC Phase I study in August 2017 with the goal of investigating the safety and pharmacokinetics (PK) of two AP-CBD/THC formulations compared to Sativex (GW Pharmaceuticals), a cannabis extract formulated for buccal delivery that contains both CBD and THC in a randomized three-way crossover design that enrolled 21 healthy volunteers.

The company reported significant improvements in the PK of AP-CBD/THC compared to Sativex with an improvement of CBD exposure by 290% to 330% and THC exposure by 25% to 50%. It is difficult to speculate as to the reason for the increased exposure as there are multiple factors involved including different route of administration and different doses, but these data demonstrate that AP-CBD/THC had more than sufficient exposure of these molecules to reach pharmacologically relevant concentrations. An interesting finding from the study was that the AP-CBD/THC formulation showed a reduction in formation of THC metabolites of 25% or greater, which suggests that the rate of THC metabolism is reduced compared to Sativex. This is interesting considering that any THC delivered buccally will avoid first pass metabolism in the liver, whereas AP-CBD/THC is purely oral and cannot avoid hepatic exposure. This suggests some degree of non-linearity in the metabolism of THC, although the precise mechanism is unknown at this time. Moreover, Intec reported that the drug was safe and well tolerated, with no serious adverse effects, although this is not particularly surprising given the well understood safety profile of these molecules.

The two indications being pursued by the company were neuropathic low back pain and fibromyalgia, although it has made no commitments to study either. Both neuropathic low back pain and fibromyalgia are exceptionally large markets with a high degree of unmet medical need. Although both of these indications can be described as pain disorders, their etiologies are significantly different. Furthermore, the company recently stated that it is in the process of redesigning the AP for CBD/THC to improve efficacy and plans to initiate another Phase I to evaluate the PK of the revamped drug. It has not provided insight into when the trial will begin. For these reasons, we do not include the AP-CBD/THC programme in our valuation at this time.

Sensitivities

Because Intec is developing reformulations of approved pharmaceuticals for its original indications and the efficacy of these compounds is not under question, many of the development risks typically associated with pre-commercial pharmaceutical companies are mitigated in this case. However, the data supporting the clinical benefit of the AP technology over other formulations are limited. The potential benefit appears most pronounced in the case of AP-CDLD, in which the pharmacokinetics of levodopa support a gastroretentive formulation. This translated into better improvements in off time than the recently approved controlled release formulation Rytary. However, this effect required supplementation with additional immediate release levodopa pills, meaning that AP-CDLD alone may perform worse, although the Phase III permits an increased dosing frequency (three times a day), which may mitigate this risk.

The company will face significant commercial risks as AP-CDLD is entering an especially competitive market where potentially disruptive technology is being developed. AP-CDLD is a viable solution to the difficulties in levodopa-based therapy, but there are two products already available and others in various development stages. Additionally, there are marketed and development

products that aim to achieve better disease control by using an alternative route of administration (ie the Duopa duodenal pump). Finally, the advancement of COMT inhibitors may further improve the pharmacokinetic profile of levodopa and limit the benefits of AP-CDLD over other formulations.

Valuation

We have decreased our valuation to NIS619m ($176m) or NIS23.85 ($6.79) per basic share from NIS737m ($205m) or NIS28.39 ($7.91) per basic share. This reduction is mainly attributed to the removal of the AP-ZP programme for the treatment of insomnia from our valuation as the company has stated it is currently concentrating its resources towards the AP-CDLD and AP-CBD/THC development programmes. The change is also driven by the increase in development costs associated with the AP-CDLD programme due to enrolment expansion, which delays complete enrolment to Q318 (previously Q417) and launch year to 2020 (previously 2019), and lower net cash. The AP-CDLD programme constitutes approximately 75% of Intec's total valuation, corresponding to $247m in combined peak sales in the US and Europe. These effects were offset by increasing our US price growth rate assumption from 2% to 4% based on current pharmaceutical industry pricing power specifically within Parkinson's disease and rolling forward our NPVs. We do not include the AP-CBD/THC programme in our valuation as the precise target indication has not been announced. However, we find the Phase I clinical results to be encouraging and expect to add this programme to our valuation with more details following the completion of the Phase I trial for the redesigned AP-CBD/THC. We also expect to update our valuation with the release of data from the Phase III study of AP-CDLD in 2019.

Exhibit 5: Valuation of Intec Pharma

Development Program	Clinical stage	Prob. of success	Launch year	Launch Pricing ($)	Peak sales ($m)	Patent/Exclusivity Protection	Royalty/ Margin	rNPV (NISm)
AP-CDLD, US	Phase III	60%	2020	8,200	140	2029	47%	299
AP-CDLD, Europe	Phase III	60%	2020	4,900	107	2029	40%	191
AP-CDLD development costs	Phase III							-28
Unallocated costs (administrative costs, etc.)								-69
Total								392
Net cash and equivalents (30 September 2017) (NISm)								227
Total firm value (NISm)								619
Total basic shares (m)								26.0
Value per basic share (NIS)								23.85
Options (m)								0.1
Total diluted shares (m)								26.1
Value per diluted share (NIS)								23.72

Source: Intec reports, Edison Investment Research

Financials

Intec reported a loss of $7.4m for Q317. This increase compared to Q316 ($3.3m) is due to the approximate 40% increase in R&D expenses associated with the AP-CDLD Phase III trial, the absence of capital from the Israel Innovation Authority (IIA) to offset R&D, and the 50% increase in general administrative expenses. Additionally, the company is expanding enrolment for the AP-CDLD Phase III trial to 420 patients (after downsizing enrolment to 328 from 460 patients in July of this year), which is due to a change in statistical assumptions. We have therefore increased our expected R&D spending for 2017 to $19.4m from $17.1m. The company ended the period with $65m in cash and equivalents, which was supplemented by the August 2017 public offering of $57.5m. We believe that this is sufficient capital for the company to break even, which we estimate will be in 2020.

Exhibit 6: Financial summary

$000s	2015	2016	2017e	2018e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	0	0	0	0
Cost of Sales	0	0	0	0
Gross Profit	0	0	0	0
Research and development	(4,815)	(10,749)	(19,412)	(13,987)
Selling, general & administrative	(2,788)	(3,097)	(4,381)	(4,819)
EBITDA	(8,330)	(14,513)	(24,133)	(19,188)
Operating Profit (before amort. and except.)	(7,584)	(13,812)	(23,627)	(18,640)
Intangible Amortisation	0	0	0	0
Exceptionals/Other	0	0	0	0
Operating Profit	(7,584)	(13,812)	(23,627)	(18,640)
Net Interest	404	450	450	450
Other (change in fair value of warrants)	0	0	0	0
Profit Before Tax (norm)	(7,180)	(13,362)	(23,177)	(18,190)
Profit Before Tax (IFRS)	(7,180)	(13,362)	(23,177)	(18,190)
Tax	0	0	0	0
Deferred tax	0	0	0	0
Profit After Tax (norm)	(7,180)	(13,362)	(23,177)	(18,190)
Profit After Tax (IFRS)	(7,180)	(13,362)	(23,177)	(18,190)
Average Number of Shares Outstanding (m)	7.8	11.4	26.5	27.8
EPS - normalised (c)	(92.16)	(116.72)	(87.52)	(65.41)
EPS - IFRS ($)	(0.92)	(1.17)	(0.88)	(0.65)
Dividend per share (c)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	4,076	4,047	4,385	4,714
Intangible Assets	0	0	0	0
Tangible Assets	4,076	4,047	4,385	4,714
Other	0	0	0	0
Current Assets	33,096	20,674	64,330	46,228
Stocks	0	0	0	0
Debtors	2,361	2,384	1,333	1,333
Cash	30,673	18,228	62,929	44,827
Other	62	62	68	68
Current Liabilities	(614)	(1,152)	(1,921)	(1,519)
Creditors	(614)	(1,152)	(1,921)	(1,519)
Short term borrowings	0	0	0	0
Long Term Liabilities	(327)	(97)	0	0
Long term borrowings	0	0	0	0
Other long term liabilities	(327)	(97)	0	0
Net Assets	36,231	23,472	66,793	49,423
CASH FLOW				
Operating Cash Flow	(7,931)	(12,005)	(18,356)	(17,225)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(1,384)	(482)	(843)	(877)
Acquisitions/disposals	0	206	254	0
Financing	32,452	0	63,675	0
Dividends	0	0	0	0
Other	13	0	0	0
Net Cash Flow	23,150	(12,281)	44,729	(18,103)
Opening net debt/(cash)	(7,742)	(30,673)	(18,228)	(62,899)
HP finance leases initiated	0	0	0	0
Exchange rate movements	(232)	8	(58)	0
Other	13	(172)	0	0
Closing net debt/(cash)	(30,673)	(18,228)	(62,899)	(44,797)

Source: Intec Pharma reports, Edison Investment Research

Contact details	Revenue by geography
12 Hartomst. (RMPE building) P.O.Box 45219 Jerusalem 91450 Israel +97225864657 http://intecpharma.com/	N/A

Management team

CEO and Vice Chairman: Jeffrey A Meckler	CFO: Nir Sassi
Mr Meckler has been the CEO of Intec since July 2017. Prior to serving as the CEO, he served as the vice chairman of the board of directors from April 2017. Prior to Intec, Mr Meckler spent over 17 years at Pfizer in leadership roles and most recently served as the CEO of Cocrystal Pharma.	Mr Nir Sassi has been the CFO of Intec since August 2016. Prior to serving as the CFO, he served as the VP of finance commencing in March 2010. Prior to Intec, Mr Sassi served as a senior manager at PricewaterhouseCoopers Israel from 2002 until 2010.
Chairman: John W Kozarich	**COO: Nadav Navon**
Dr Kozarich has nearly 40 years of experience in the biopharmaceutical industry and academia. Dr Kozarich currently serves as chairman of Ligand Pharmaceuticals, and chairman and president of ActivX Biosciences. Prior to his role as chairman, Dr Kozarich was vice president at Merck.	Dr Nadav Navon has been with Intec since March 2006 and has served as the COO since July 2017. Before that he served as the executive vice president of research & development and operations from March 2015 and as the vice president of research & development and operations from May 2013.

Principal shareholders	(%)
Acuta Capital Partners LLC	10.45
venBio Select Advisor LLC	8.42
Adage Capital Partners Gp LLC	6.62
EcoR1 Capital LLC	5.75
Cormorant Asset Management LLC	3.11

Companies named in this report

AbbVie (ABBV), Acorda Therapeutics (ACOR), Bristol-Myers Squibb (BMY), Dainippon Sumitomo (TYO:4506), Depomed (DEPO), GlaxoSmithKline (GLK), Impax Laboratories (IPXL), Merck (MRK), Novartis (NVS), Orion (HEL:ORNBV), Sanofi (SNY)

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