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FID-007: Nanoencapsulated Paclitaxel Derived from a Novel Nano-Drug Delivery Platform

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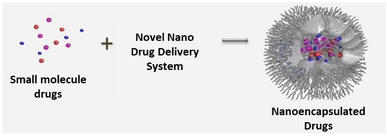
Background

Fulgent is developing a polymer-based, nano-encapsulating drug delivery platform to potentially enhance safety and efficacy through improvements in:

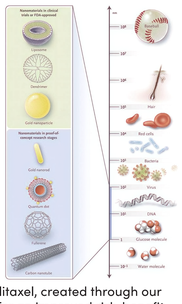
- Solubility and absorption, which could improve the pharmacokinetics (PK) profile
- Applicability to both IV and oral drug delivery formulations
- Development timeline
- Simplified and lower-cost production

A plug-and-play drug delivery platform would also have the potential advantage of providing "multiple shots on goal." To illustrate the nano-encapsulating drug delivery concept, a cartoon schematic is shown below:



This proprietary and patented technology makes poorly soluble drugs water soluble by encapsulating them with nanoparticles composed of polyethyloxazoline (PEOX) polymers. Improved solubility has the potential to improve pharmacokinetics, reduce toxicity, and enhance an active ingredient's effect. Importantly, these polymers have been fully tested in GLP toxicity studies using both rodents and non-human primates.

What is Nanomedicine & the Nanoparticle Advantage?

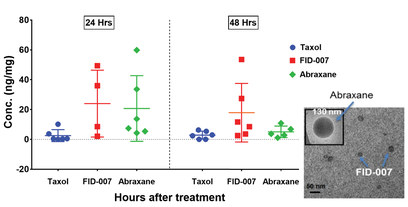


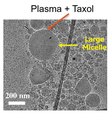
Nanomedicine is the application of nano-technology to medicine (i.e. 1-100 nm). Encapsulating an active drug ingredient with nanoparticles is one example of how nanomedicine may improve efficacy or safety by improving solubility of drugs that are not readily soluble but have known therapeutic benefits. For example, paclitaxel is a drug widely utilized in cancer treatment but is known to have poor solubility, which likely hampers its clinical efficacy. We hypothesize that a more water-soluble formulation of paclitaxel, created through our proprietary technology, would offer an improved risk-benefit profile. Our lead investigational drug FID-007 is a novel, nanoencapsulated formulation of paclitaxel that is designed to test this hypothesis.

In Vitro / In Vivo Data

FID-007: Mouse Xenograph Study Shows Greater Uptake in Tumor Tissue:

Paclitaxel Concentrations in Mouse Tumor Tissue

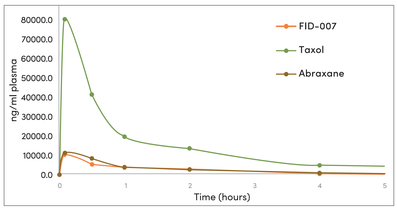




- FID-007 is significantly smaller in size than Taxol and slightly smaller than Abraxane[1]
- Data from one study in mice indicated that FID-007 is found in higher concentrations within tumor tissue after administration than Taxol or Abraxane. This suggests more successful penetration of the mouse tumor tissue by FID-007.

[1] The size data for Abraxane and Taxol were obtained from Abraxis ODAC briefing package, 2006.

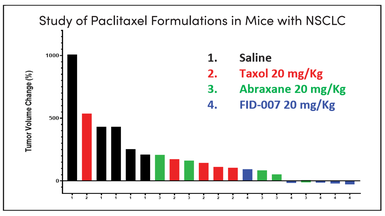
Initial *in vitro* and *in vivo* studies of our lead candidate FID-007 have shown significant differences in drug solubility in water, maximum tolerated dose (MTD - mouse), and antineoplastic effect using the PEOX nanoencapsulated paclitaxel.



The graph above depicts the pharmacokinetics (PK) profile of FID-007, Abraxane and paclitaxel from Taxol in normal mouse plasma. This data shows that the Cmax of FID-007 and Abraxane are very similar, but that the paclitaxel concentration (from Taxol) is higher after a single intravenous (IV) administration of 20 mg/kg dose, for each, respectively.

Reduced Tumor Volumes in Mouse Xenograft NSCLC Study

The following study was conducted using twenty male severe combined immunodeficiency disease (SCID) mice inoculated with 2 x 10^6 human lung cancer Calu-3 cells in the left and right hind flank. Total tumor volume for each mouse was measured after 7 to 9 days of tumor establishment broken out to 4 study groups each of which consisting of n=5. Using saline as the control, dosages of Taxol (20 mg/kg), Abraxane (20 mg/kg), and FID-007 (20 mg/kg) were prepared and administered IV through the tail vein on days 1,8,15, and prior to terminal euthanasia on day 20. The graph below presents the tumor volume change as a percentage from baseline.



Similar results were also observed in several other xenograph studies in which FID-007 reduced or limited tumor growth in several tumor types including A549 (lung), MOLT-4 (leukemia), NCI-N87 (gastric), MDA-MB-231 (triple negative breast), MIA PaCa-2 (pancreatic), and OV-90 (ovarian).

The following sections present recent clinical experience of FID-007 demonstrating a desirable tissue penetration profile and promising clinical data from this example poorly soluble, small molecule drug.

Early Clinical Data and Observations

Anticipated Clinical Risks: FID-007 is expected to have similar safety concerns as Taxol and Abraxane. All grade treatment related adverse events (TRAEs) in ≥ 25% were rash, alopecia, pruritis, anemia, leukopenia, fatigue, dysgeusia, anorexia, nausea and neutropenia. Grade 3 and/or Grade 4, TRAEs occurring in > 1% patient were anemia, neutropenia, leukopenia, and maculopapular rash. There were no treatment discontinuations due to toxicity. No other clinically significant safety information has risen during the clinical trial.

In a Phase 1 study (NCT03537690/ IND 137539) in patients with advanced solid tumors, FID-007 was evaluated in a dose escalation study at 15 mg/m^2 , with escalating dosages up to 160 mg/m^2. At this time, forty (40) patients were enrolled in cohorts evaluating FID-007 with a subset of patients providing evaluable data towards the safety and efficacy analyses. The clinical data is summarized below:

Pharmacokinetic Linearity of FID-007 Compared to Abraxane and Taxol

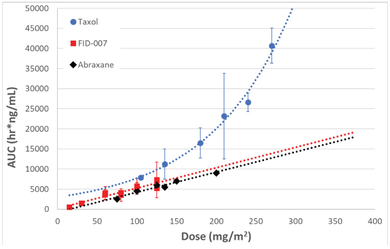


Table 1: Patient Baseline Characteristics

Characteristic	Overall, N = 40
Years of Age, Median (Range)	61 (32 - 75)
Gender	
Female	23 (58%)
Male	17 (43%)
Race/Ethnicity	
White or Caucasian	11 (28%)
Hispanic	19 (48%)
Black or African American	1 (3%)
Asian (including Indian)	9 (23%)
ECOG PS	
0	11 (28%)
1	28 (70%)
2	1 (3%)
Number of Prior Regimens, Median (Range)	2 (1 - 5)

Table 2: Dose Levels Evaluated

Dose Level	FID-007 (mg/m2)	No. of Patients	No. of Evaluable Patients	DLTs Observed	DLT Type
1	15	3	3	0	
2	30	3	3	0	
3	60	3	3	0	
4	80	3	3	0	
5	100	5	5	2[a]	Rash
5b	100	4	3	0	
6	125	9	6	1	Gr4 neutropenia
7	160	3	3	1	Gr3febrile neutropenia
6b[b]	125	7	6	1	Gr4 neutropenia

Pancreatobiliary	11 (28%)
Non-small cell lung	4 (10%)
Head and Neck SCC	11 (28%)
Other	14 (35%)

a. Two patients in dose level 5 had DLT of grade 3 maculopapular rash. Rash resolved with supportive care and/or dose delays in both patients and treatment was continued without recurrence of grade 3 rash. DLT definition was modified for dose levels 5b and above to allow for grade 3 rash that resolves within 7 days. No further patients had DLT for rash in the subsequent dose levels.

b. Cohort 6b used modified pre-medication by removing sodium bicarbonate infusion and addition of corticosteroid pre-medication for C1 only. One patient had to be replaced.

Table 3: Treatment-related select AE categories (>=10%)

Toxicity	Number Of Patients With Maximum Grade Toxicity Experienced		
	Grade 1 or 2	Grade 3	Grade 4
Alopecia	21 (53%)	0	0
Rash maculo-papular	16 (40%)	11 (28%)	0
Pruritus	16 (40%)	0	0
Fatigue	15 (38%)	0	0
Anorexia	12 (30%)	1 (3%)	0
Nausea	12 (30%)	0	0
White blood cell decreased	11 (28%)	5 (13%)	3 (8%)
Anemia	10 (25%)	6 (15%)	0
Dysgeusia	10 (25%)	0	0
Neutrophil count decreased	9 (23%)	3 (8%)	5 (13%)
Peripheral sensory neuropathy	9 (23%)	0	0
Dry skin	8 (20%)	0	0
Palmar-plantar erythrodysesthesia syndrome	7 (18%)	0	0
Constipation	6 (15%)	0	0
Vomiting	6 (15%)	0	0
Diarrhea	5 (13%)	0	0
Arthralgia	4 (10%)	0	0
AST	4 (10%)	0	0

Early Clinical Data and Observations (continued)

The following table presents the Tumor responses and the associated outcomes thereto. Out of the forty (40) total patients with available data, partial response (PR) was observed for 18% of the patients, 35% with steady disease (SD), and 45% showing progressive disease (PD). The duration of follow-up ranged from 0.4 to 38.9 months with a median of twelve months.

Table 4: Tumor Responses and Outcomes

Characteristic	Overall, N = 40
Total Courses Completed, Median (Range)	2 (1 - 30)
Best Response*	
PR	7 (18%)
SD	14 (35%)
PD[a]	18 (45%)
Duration of Follow-up (Months), Median (Range)	12.0 (0.4, 38.9)

a. PD includes 4 patients who had clinical deteriorations prior to RECIST evaluation.

* One patient response is pending

H&N Cancer:

- 57% Objective Response Rate (ORR) and 71% Disease Control Rate (DCR) were observed in 7 heavily treated H&N patients. Among them, 6/7 had prior Taxane treatment.

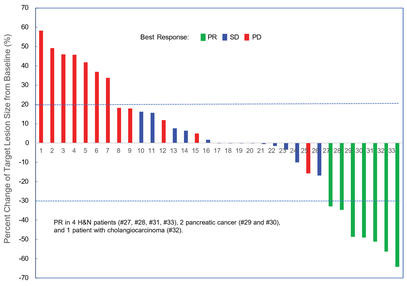
Ampullary/Pancreatic:

- 50% ORR and 75% DCR were seen in 4 heavily treated ampullary and pancreatic patients.

Waterfall Plot of Responses to FID-007

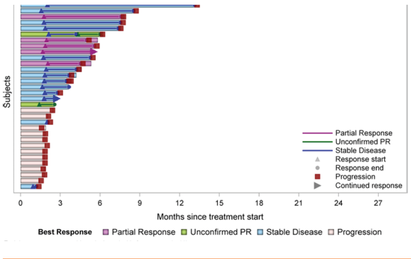
The preliminary efficacy from patients treated with FID-007 displayed as a waterfall plot is shown in the figure below.

Waterfall Plot for Best Response by Patient



The Phase I preliminary clinical data is further illustrated below displayed as a swimmer plot for responses over time:

Swimmer Plot for Responses Over Time



Conclusions

FID-007 Phase I First in Human Clinical Trial – Preliminary Findings (n=40 patients):

- Dose levels up to 160 mg/m2/week with potentially a manageable safety profile, RP2D at 125 mg/m2/week.
- There is preliminary evidence of anti-tumor activity in 40 heavily pre-treated patients across different tumor types (ORR = 18%):
  - Within the 7 heavily treated H&N patients, the ORR was 57%, of which 6/7 had prior Taxane treatment.
  - Within the 4 heavily treated Ampullary/Pancreatic patients, the ORR = 50%.
- No high-grade neuropathy adverse events, which is often seen in other taxane regimens.
- Potential shortening of the developmental timelines for other poorly soluble drugs may be delivered through a PEOX nanoparticle platform.