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ORIGINAL

# First clinical trial of a novel caspase inhibitor: anti-apoptotic caspase inhibitor, IDN-6556, improves liver enzymes

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**Key words**
apoptosis – caspase inhibitor – normal volunteers – hepatic impaired patients

**Abstract.** Objective: To evaluate the safety of IDN-6556, a novel anti-apoptotic pan-caspase inhibitor, administered in single and multiple ascending doses in normal volunteers and patients with hepatic dysfunction. Materials and methods: IDN-6556 was administered as a 30-minute intravenous infusion in rising doses to 3 groups: Group A, normal volunteers, given as a single infusion, Group B, normal volunteers, given q.i.d. for 7 days, Group C, patients with hepatic impairment (elevated transaminases, alanine transaminase, ALT and aspartate transaminase, AST), given q.i.d. for 7 days. Results: The drug was well tolerated up to 10 mg/kg/infusion for a single dose, and 1.5 mg/kg/infusion q.i.d. for 7 days, with the dose-limiting adverse event of phlebitis or inflammation at the site of the infusion. This toxicity was predicted from animal studies. Clinically and statistically meaningful dose-related falls in transaminases were seen in all but 1 of the hepatic impaired patients. Two-way ANOVA analyses of the changes for all the IDN-6556 groups combined versus placebo were: ALT absolute change: $p < 0.0001$ and % change: $p = 0.012$, AST absolute and % changes: $p < 0.0001$. After discontinuation of the drug (after 7 days of dosing), the transaminases rapidly returned to the pre-treatment levels. Conclusions: Following intravenous administration of a novel anti-apoptotic caspase inhibitor, adverse events were mild-to-moderate in severity, resolved in a few days and did not result in any subject terminating treatment prematurely. The effects in hepatic impaired patients appear to be consistent with both the administration and subsequent abrupt withdrawal of an effective hepatoprotective drug that delays cell death in hepatocytes.

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## Introduction

Apoptosis, a ubiquitous biological process also known as programed cell death, occurs after a cascade of intracellular enzymes (the caspases) is activated. Drugs that can inhibit apoptosis have the potential to maintain normal function in tissues with excessive apoptosis following a pathological insult. IDN-6556 is a novel small molecule, irreversible caspase inhibitor that prevents apoptosis; it is believed to be the first anti-apoptotic caspase inhibitor to enter clinical trials. There are numerous caspases that exist in slightly different forms and IDN-6556 is a potent, selective inhibitor of all the key enzymes, including caspases 1, 3, 6, 7, 8 and 9. Caspases are synthesized as inactive procaspases, which become active after proteolytic cleavage. IDN-6556 is a selective enzyme inhibitor and binds to and inhibits activated caspases only.

In addition to normal housekeeping functions in the liver, apoptosis is believed to play a role in a number of hepatic diseases (reviewed in [Galle et al. 1995, Patel and Gores 1995]). These diseases include alcoholic hepatitis [Natori et al. 2001, Ziol et al. 2001], hepatitis B and C (HBV, HCV) [Bantel et al. 2001, Pianko et al. 2000] and ischemia/reperfusion injury associated with liver transplant [Gao et al. 1998, Natori et al. 1999].

IDN-6556 was shown to prevent apoptosis in a number of cellular assays and to be effective in animal models of liver disease and dysfunction. In vivo, caspases are activated during apoptosis and before an elevation of liver enzymes in plasma indicative of liver damage. IDN-6556 was evaluated for efficacy in 2 acute animal models of cytokine-mediated hepatic cell apoptosis. These models include using an agonistic antibody to the Fas ligand to produce a fulminant hepatitis within hours, and a lipopolysaccharide/d-ga-

lactosamine model of hepatitis. In both these models, the compound was effective at submilligram doses per kilogram body weight. The data suggest that IDN-6556 is equally efficacious when dosed i.v. (intravenous), p.o (oral), i.m. (intramuscular), or i.p. (intraperitoneal) [Hoglen et al. 2003].

IDN-6556, administered intravenously, was tested for subacute toxicity in rats and monkeys in a number of studies. The major dose-limiting toxicity was inflammation in the veins used for the infusions. This phlebitis was related to dose, concentration and duration of exposure. The terminal plasma half-life ($t_{1/2}$) in rats and monkeys is approximately 1 – 2 hours.

This study is the first in which the drug was given to human normal volunteers and hepatic impaired patients. Its objectives were to determine the safety, tolerability and pharmacokinetics of IDN-6556 after single- and multiple-dose administration.

## Methods

### Ethics

The study was approved by the Independent Investigation Review Board (Plantation, FL). The IRB gave prior approval for the start of each dosing group after review of data.

### Study population

The study was divided into 3 parts. The first part (Part A) consisted of a rising dose study of a single 30-minute intravenous infusion, with a 10-day follow-up in normal volunteers. The second part (Part B) consisted of a rising dose study of 30-minute intravenous infusions, q.i.d. for 7 days, with a 14-day follow-up in normal volunteers. The third part of the study (Part C) consisted of a rising dose study of 30-minute intravenous infusions, q.i.d. for 7 days, with a 7-day follow-up in stable, hepatic impaired outpatients. Study participants were admitted to an inpatient unit throughout the dosing period and for several days afterwards.

Five cohorts of 6 subjects (5 active drug, 1 saline placebo) were planned for Parts A and B. Five cohorts of 5 patients (4 active drug, 1 saline placebo) were planned for Part C. The key inclusion and exclusion criteria are given in Table 1.

### Treatment/dose escalation

The drug was administered as a 30-minute intravenous infusion. Each vial of IDN-6556 was reconstituted with 5 ml of sterile water for injection. The appropriate dose calculation was made for each dosing group and subject, based on weight, and the appropriate volume of reconstituted drug was added to a 100 ml bag of sterile saline for injection. Exactly halfway through the 0.5 mg/kg dosing group in Part B, the protocol was amended to determine if an increased infusion volume would mitigate vein irritation and phlebitis: the volume of sterile saline was increased from 100 to 500 ml, and at least 50 ml of sterile saline was administered after dosing to flush the infusion administration set and veins.

Subjects in the B5 dosing group received a 1.0 mg/kg dose of IDN-6556 administered as a rapid intravenous injection with no dilution of study medication into sterile saline. This was supposed to be followed by a rapid flush of 500 ml of saline; in fact, the post-drug flush was administered over 30 minutes. Since the symptoms of phlebitis were no better than with prior regimens, no further doses were given to these subjects. The actual doses administered in each of the 3 parts of the study are given in Table 2.

### Protocol amendments

As described above, the protocol was amended to increase the dilution of study drug to 500 ml during the 0.5 mg/kg dosing group in Part B. This amendment applied to all subsequent infusions, with exception of the rapid infusion group B5.

The protocol was amended to exclude patients with HCV infection in Part C after dosing with 0.1 mg/kg, as increases in transaminases over baseline were seen after dosing had finished in some patients (see below).

### Endpoints and analysis

Study drug safety and tolerability were assessed by recording all potential adverse

Table 1. Major inclusion/exclusion criteria.

| Inclusion for Parts A and B | Exclusion for Parts A and B |
|---|---|
| Age: 18 – 60 years of age | If female: pregnant, lactating or positive serum pregnancy test |
| Generally healthy | Presence of clinically significant illness or abnormality |
| If female: either surgically sterile or post-menopausal or using acceptable double barrier, non-hormonal contraception | Presence or history of illness affecting absorption, distribution, metabolism or elimination of the study drug |
| Written informed consent. Understand and comply with the requirements of the study | Clinically significant elevations of liver function tests (ALT, AST, γ-GT, bilirubin, or alkaline phosphatase > 1.5 × ULN, or NCI Grade 1 toxicity) |
| | Presence or history of alcohol or drug abuse ≤ 90 days or positive urine drug screen |
| | Any investigational drug ≤ 30 days |
| | HIV, HCV or HBV infection |
| **Additional inclusion for Part C** | **Additional exclusion for Part C** |
| Prior diagnosis of compensated liver impairment, stable indicators of liver impairment (NCI Grade 1) for 2 months | HIV positive |
| Projected survival > 6 months | Severe hepatic encephalopathy (Grade 2 or above) or delirium tremens |
| | Severe congestive heart failure |
| | Renal impairment or hepatorenal syndrome (creatinine > 1.5 mg/dl) |
| | Acute pancreatitis (serum amylase and lipase > 3 normal, NCI Grade 3 toxicity) |
| | Hospitalization for liver disease within 60 days |
| | Changes in laboratory values (liver and coagulation panels) > 2 normal, or greater than Grade 2 NCI toxicity |
| | Prothrombin time > 3 s above control |
| | Bilirubin levels > 5 mg per 100 ml |
| | Any malignancy |

ULN = upper limit of normal.

event parameters. Vital signs, physical findings and clinical laboratory test (hematology, urinalysis, blood chemistry) were frequently recorded. The pharmacokinetics of IDN-6556 were evaluated through analysis of serum and urine specimens collected at specified timepoints.

The data were summarized by means and standard error of the mean (SEM). Pharmacokinetic parameters were assessed by data listings and calculations of summary statistics. Two-way analysis of variance (ANOVA) was performed for the assessment of changes in laboratory values for Part C (SAS version 8.2, SAS Institute, Cary, NC).

## Results

### *Demographics and baseline characteristics*

A total of 76 subjects was evaluated in this study, 60 normal volunteers and 16 patients (Table 2). Demographics are shown in Table 3.

The initial laboratory values for normal volunteers were all within the normal range, as specified in the protocol. Although the protocol allowed patients with significant hepatic disease to participate in the trial in Part C (Table 1), in fact the patients who entered the

Table 2. Dose levels administered.

| Part A | | | Part B | | | Part C | | |
|---|---|---|---|---|---|---|---|---|
| Dose level (mg/kg) | Active drug (N) | Placebo (N) | Dose level (mg/kg) | Active drug (N) | Placebo (N) | Dose level (mg/kg) | Active drug (N) | Placebo (N) |
| 0.1 | 5 | 1 | 0.1 | 5 | 1 | 0.1 | 4 | 1 |
| 0.5 | 5 | 1 | 0.5 | 5 | 1 | 0.5 | 4 | 2 |
| 1.0 | 5 | 1 | 1.0 | 5 | 1 | 1.0 | 3 | 2 |
| 5.0 | 5 | 1 | 1.5 | 5 | 1 | – | – | – |
| 10.0 | 5 | 1 | 1.0* | 5 | 1 | – | – | – |
| Total N | 25 | 5 | | 25 | 5 | | 11 | 5 |

* = the dosing regimen for this cohort consisted of a rapid infusion of study drug followed by 500 ml saline

Table 3. Demographics.

| Group and treatment (mg/kg) | N | Gender (M/F) | Age in years (Mean) | Race | | |
|---|---|---|---|---|---|---|
| | | | | Caucasian | Black | Hispanic |
| A 0.1 | 5 | 2/3 | 41.8 | 0 (0%) | 0 (0%) | 5 (100%) |
| A 0.5 | 5 | 3/2 | 38.0 | 0 (0%) | 0 (0%) | 5 (100%) |
| A 1.0 | 5 | 2/3 | 30.8 | 0 (0%) | 1 (20%) | 4 (80%) |
| A 5.0 | 5 | 3/2 | 40.0 | 0 (0%) | 0 (0%) | 5 (100%) |
| A 10.0 | 5 | 3/2 | 30.2 | 0 (0%) | 0 (0%) | 5 (100%) |
| A placebo | 5 | 2/3 | 35.8 | 0 (0%) | 0 (0%) | 5 (100%) |
| B 0.1 | 5 | 2/3 | 32.8 | 1 (20%) | 1 (20%) | 3 (60%) |
| B 0.5 | 5 | 3/2 | 44.0 | 0 (0%) | 0 (0%) | 5 (100%) |
| B 1.0 | 5 | 2/3 | 29.8 | 0 (0%) | 0 (0%) | 5 (100%) |
| B 1.5 | 5 | 4/1 | 35.2 | 0 (0%) | 1 (20%) | 4 (80%) |
| B 1.0* | 5 | 3/2 | 42.6 | 0 (0%) | 0 (0%) | 5 (100%) |
| B placebo | 5 | 3/2 | 43.6 | 0 (0%) | 0 (0%) | 5 (100%) |
| C 0.1 | 4 | 3/1 | 44.5 | 1 (25%) | 0 (0%) | 3 (75%) |
| C 0.5 | 4 | 3/1 | 30.0 | 0 (0%) | 0 (0%) | 4 (100%) |
| C 1.0 | 3 | 3/0 | 40.0 | 0 (0%) | 0 (0%) | 3 (100%) |
| C placebo | 5 | 3/2 | 39.6 | 0 (0%) | 0 (0%) | 5 (100%) |

* = the dosing regimen for this cohort consisted of a rapid infusion of study drug followed by 500 ml saline flush.

study had only mild hepatic impairment with transaminase elevations as the only significant marker of hepatic impairment. No patients had elevations in their prothrombin times or serum bilirubin concentrations. Table 4 lists the diagnoses of the patients in Part C by dosage group (some patients had > 1 diagnosis in Group 1).

## Safety

No normal volunteer or patient discontinued the study because of adverse events. There were no serious adverse events. Adverse events tended to be of mild-to-moderate severity and of relatively short duration. The principal adverse events were those related to vein inflammation (i.e. phlebitis) following infusion or bolus administration of IDN-6556 and leukocytosis. The incidence and nature of phlebitis in Part A of the study provided sufficient cause to reduce dose escalation in Parts B and C. A table of the most frequent adverse events is given in Table 5 below.

The vein irritation (phlebitis) was clearly both drug- and dose-related. It was also related to the drug concentration as the inci-

Table 4. Baseline characteristics and subject disposition of patients in part C.

| Diagnosis | Group 1 (N) | | Group 2 (N) | | Group 3 (N) | |
|---|---|---|---|---|---|---|
| | 0.1 mg/kg | Placebo | 0.5 mg/kg | Placebo | 1.0 mg/kg | Placebo |
| HCV | 3 | 1 | | | | |
| Alcoholic liver disease | 2 | | | | | |
| Fatty liver | | | 1 | | | |
| No known diagnosis | 1 | | 3 | 2 | 3 | 2 |

Table 5. Adverse event frequency.

| Adverse event | Group A | | | | Group B | | | | Group C | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (preferred term) | Active (N = 25) | | Placebo (N = 5) | | Active (N = 25) | | Placebo (N = 5) | | Active (N = 11) | | Placebo (N = 5) | |
| | N | (%) | N | (%) | N | (%) | N | (%) | N | (%) | N | (%) |
| Phlebitis | 6 | (24) | 0 | (0) | 21 | (84) | 0 | (0) | 5 | (45) | 0 | (0) |
| Vein pain* | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 5 | (45) | 3 | (60) |
| Headache | 2 | (8) | 1 | (20) | 14 | (56) | 2 | (40) | 3 | (27) | 2 | (40) |
| Fever | 1 | (4) | 0 | (0) | 5 | (20) | 0 | (0) | 0 | (0) | 0 | (0) |
| Leukocytosis | 4 | (16) | 0 | (0) | 2 | (8) | 0 | (0) | 0 | (0) | 0 | (0) |
| Back pain | 1 | (4) | 0 | (0) | 3 | (12) | 0 | (0) | 0 | (0) | 0 | (0) |
| Nausea | 0 | (0) | 0 | (0) | 3 | (12) | 0 | (0) | 0 | (0) | 1 | (20) |
| Taste perversion | 0 | (0) | 0 | (0) | 3 | (12) | 0 | (0) | 0 | (0) | 0 | (0) |
| Abdominal pain | 1 | (4) | 0 | (0) | 2 | (8) | 0 | (0) | 0 | (0) | 0 | (0) |
| Dizziness | 2 | (8) | 0 | (0) | 0 | (0) | 0 | (0) | 1 | (9) | 0 | (0) |
| Upper respiratory infection | 2 | (8) | 1 | (20) | 0 | (0) | 0 | (0) | 1 | (9) | 0 | (0) |
| Glucose tolerance abnormal | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 2 | (18) | 0 | (0) |
| Constipation | 0 | (0) | 1 | (20) | 0 | (0) | 0 | (0) | 1 | (9) | 1 | (20) |
| Myalgia | 0 | (0) | 0 | (0) | 2 | (8) | 0 | (0) | 0 | (0) | 0 | (0) |
| Other** | 3 | (12) | 1 | (20) | 11 | (44) | 1 | (20) | 4 | (36) | 2 | (40) |

* = recorded only in Part C, ** = other constitutes single reports of the following adverse events: Group A flatulence, glycosuria and rash; Group B allergic reaction, diarrhea, dyspepsia, furunculosis, dry lips, lymphadenopathy, paroniria, pharyngitis, skin disorder, skin dry, urinary incontinence, urinary tract infection; Group C application site edema, chest pain, hypertension, increased stool frequency, hepatic function abnormal, skeletal pain.

dence of phlebitis decreased when the infusion volume was increased: in the 0.5 mg/kg subjects in Part B the incidence decreased from 4/5 subjects to 1/5 subjects when the dilution was increased to 500 ml in the middle of the 1-week dosing period. Phlebitis and pain did not typically occur during the infusion and usually developed several hours after the infusion in the single-dose groups (Part A) and often after several days of dosing in the multiple dose groups (Parts B and C). In a couple of patients in Parts B and C, the phlebitis did not develop until the day after all dosing had stopped. The severity of the phlebitis was not sufficient for any participant to request dosing to be interrupted, although care was taken not to administer higher doses of the drug. In Part C, the investigator differentiated between phlebitis and vein pain. While the phlebitis was dose-related, pain in the infusion vein was not clearly drug-related (Table 5).

No significant changes were observed in any laboratory parameters, including the transaminases (Figure 1), during dosing in the normal volunteers, with the exception of white blood cell counts, which showed transient increases in subjects receiving the high-

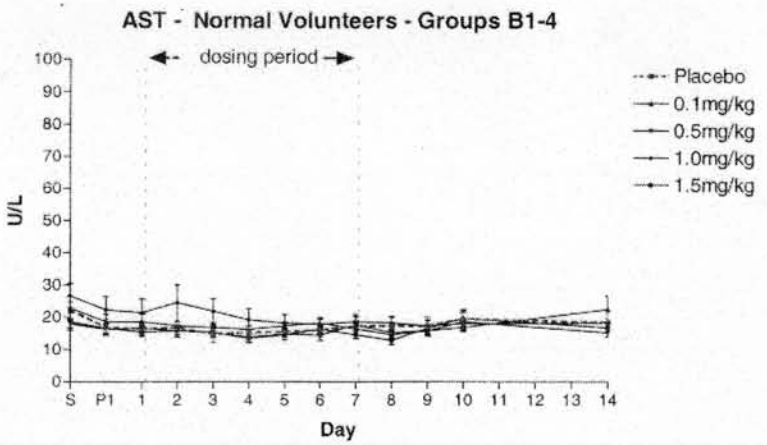


Figure 1. Mean (± SEM) values for AST are shown for the normal volunteer groups that received 7 days of dosing.

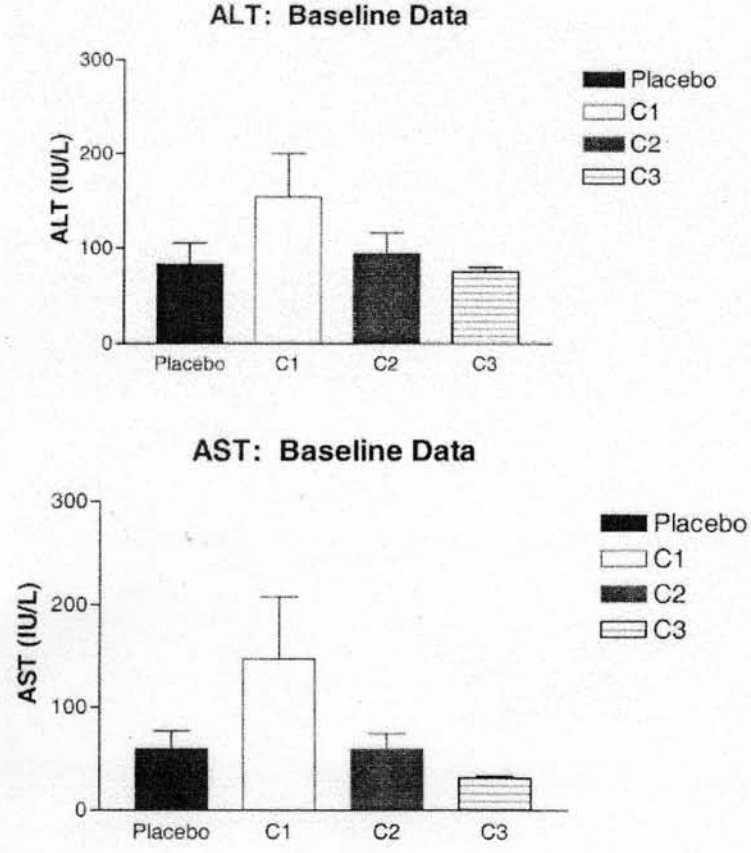


Figure 2. Mean (± SEM) baseline values for ALT (top) and AST (bottom) are shown for each cohort of patients.

est single doses (5 and 10 mg/kg). Values were just above the upper limit of normal in the 10 mg/kg group, and in the "bolus" 1 mg/kg group in Part B. The leukocytosis was neutrophilic and occurred only in subjects with phlebitis. The timing of the pyrexia, which was mild, was not well correlated with the development of phlebitis. No subject had leukocytosis or pyrexia in the absence of phlebitis; many subjects had phlebitis without accompanying leukocytosis or pyrexia. No leukocytosis or pyrexia occurred in the patients (Group C, 0.1 – 1.0 mg/kg). No significant changes in clinical laboratory tests were observed in the hepatic impaired population except for reductions in transaminase values, which are discussed below. Two patients had mildly elevated blood glucose levels and glucose tolerance tests at various times during the study; however, both had elevated fasting blood glucose levels before the study started.

## *Pharmacokinetics*

Maximum plasma concentrations of IDN-6556 ($T_{max}$) occurred at the first sampling point post infusion at 0.5830 hours when the drug was given for 1 or more doses in Parts A, B and C in all but 1 subject. In the single dose groups in Part A, plasma concentrations of IDN-6556 then declined with an approximate mean apparent terminal half-life of 1.7 – 3.1 hours. The extent of systemic exposure, assessed by $AUC_{(0-\infty)}$ and $C_{max}$, tended to increase approximately proportionately with increasing single doses of 0.1 to 1 mg/kg IDN-6556, and in a non-proportional fashion at doses of 5 mg/kg and 10 mg/kg. Following multiple intravenous doses of IDN-6556 in Parts B and C, there was no evidence of accumulation of IDN-6556 over the 7-day dosing period. In addition, for each increase in dose level in Part B, mean dose-adjusted $AUC_{last}$ and $C_{max}$ values increased in a dose-proportional fashion over the doses studied (0.1 – 1.5 mg/kg). In Part C, the extent of systemic exposure, assessed by $AUC_{last}$ and $C_{max}$, increased approximately proportionately with increasing doses of 0.1 to 0.5 mg/kg and slightly less than proportionally from 0.5 to 1 mg/kg (data not shown).

## *Laboratory evaluations Part C*

Clinically and statistically significant reductions in transaminases were observed during the 7-day treatment period in the 3 hepatic impaired dosing groups that received IDN-6556 compared to placebo, although there

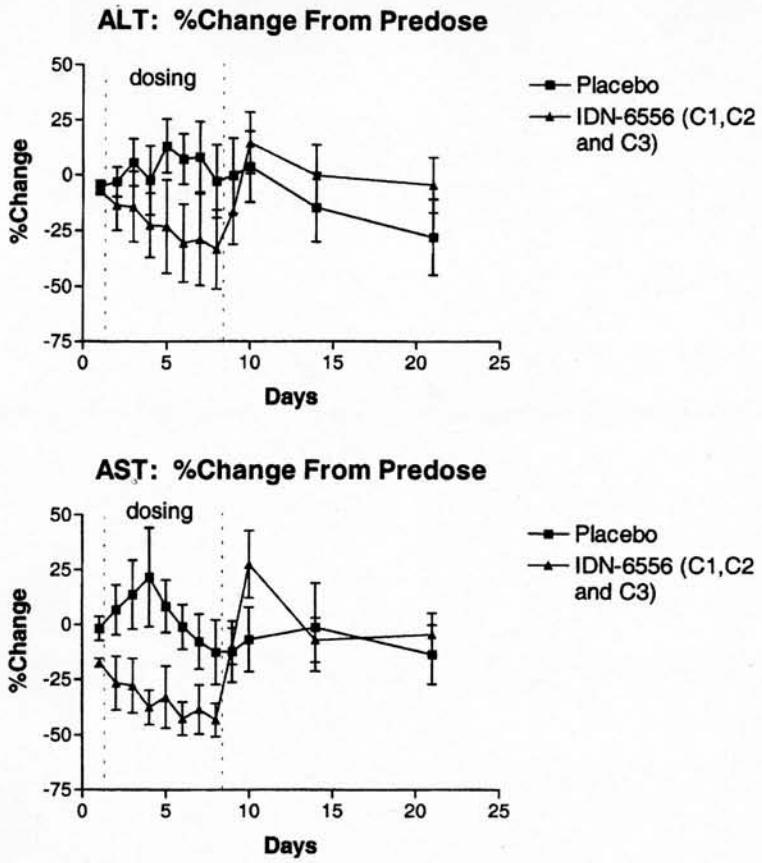


Figure 3. (top). The % change in alanine transaminase (ALT) levels is presented for all placebos (n = 5) combined, versus all drug-treated patients in groups C1, C2 and C3 (n = 11) combined; bottom: the % change in aspartate transaminase (AST) levels is presented for all placebos (n = 5) combined, versus all drug-treated patients in groups C1, C2 and C3 (n = 11) combined. Drug treatment is from Days 0 – 7. Means (± SEM) are shown.

were no statistically significant differences in ALT and AST levels between the groups at baseline (Figure 2). All patients were within approximately 2 times the upper limit of normal for transaminases. Figure 3 shows the % changes from predose values in ALT and AST during treatment for all groups combined versus placebo. Similar effects were seen with the absolute changes in the transaminases. Two-way ANOVA analyses of the changes for all the combined IDN-6556 groups versus placebo were: ALT absolute change: $p < 0.0001$ and % change: $p = 0.012$, AST absolute and % changes: $p < 0.0001$.

One patient in the C3 group (1.0 mg/kg/infusion) did not respond to the treatment, and in fact, there was a transient increase in transaminase levels during treatment to a maximum of 185 (ALT)/56 (AST) (data not shown). The cause of this patient's hepatic impairment was unknown, and the patient declined follow-up evaluation. HCV assays in the 4 HCV-positive patients showed no clinically meaningful changes in the study.

At the end of the 7-day dosing period, the transaminase levels returned to the baseline levels within the course of 1 – 3 days, and in some cases there was a transient "overshoot" above baseline. The largest such effect occurred in AST values in the C2 group (Figure 4).

## Discussion

It is believed that this study with IDN-6556 is the first publication of a clinical study involving a pan-caspase inhibitor and anti-apoptotic drug. While some of the findings were expected, other data were surprising.

The safety profile seen during the study was very similar to the findings in the prior pre-clinical and toxicology studies. Intravenous administration of IDN-6556 in animals was consistently associated with phlebitis and frequently with a neutrophilic leukocytosis. These were also the main adverse events in this trial. The incidence of phlebitis was dose-dependent after both single and multiple doses (where it occurs at lower doses). Its incidence was markedly reduced with a higher infusion volume, but a rapid infusion with a slower post-infusion flush was not beneficial. The symptoms were not sufficiently severe for any of the participants to request cessation of dosing, although care was taken not to give doses above 1.5 mg/kg q.i.d. for a week, and it is likely that significantly higher doses would not have been well tolerated.

The timing of the phlebitis was interesting. In the single-dose phase, subjects typically complained of symptoms several hours after the infusion had occurred and not during the infusion itself. In the multiple-dose phases, the symptoms usually manifested several days after the infusions started. In a couple of subjects the symptoms did not start until the day after study medication was stopped. The neutrophilic leukocytosis was most obvious in subjects treated with higher single doses. Mild pyrexia was seen in some of the normal volunteers who had phlebitis,

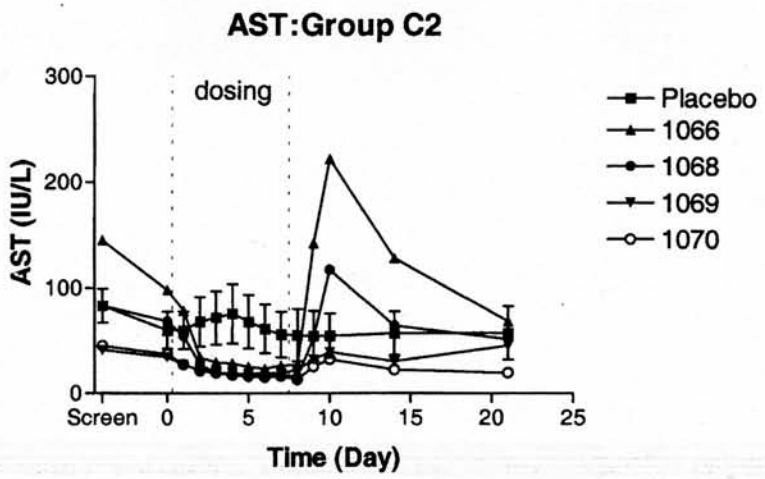


Figure 4. The AST values for the C2 patients (0.5 mg/kg/infusion) are shown individually, together with all placebo patients (n = 5, mean (± SEM)). One patient, No. 1066, had a transient increase in AST levels above previous baseline following the end of dosing with IDN-6556.

although there was no clear relationship between the timing of this and the leukocytosis. The mechanism for these probably pro-inflammatory findings has not been discovered in animals and remains speculative. However, the time course of the phlebitis suggests that it is unlikely to be a direct chemical effect of the neutral pH drug formulation and there is no obvious link to the drug's anti-apoptotic mechanism of action. Other adverse events in the study did not indicate any clear differences from placebo.

The pharmacokinetic results are consistent with a 2-compartment model of drug distribution. In animal studies, the drug is avidly taken up by the liver after intravenous or oral dosing.

This study was designed as a safety study. The clinically and statistically significant improvements in the transaminase levels were unexpected. It was not thought that the anti-apoptotic drug would have a discernable effect on the liver enzymes in patients with mild hepatic impairment. While the protocol allowed patients with significant hepatic impairment into the study, the patients who actually participated had only elevations of their transaminases and no other manifestations of hepatic dysfunction. A hepatic diagnosis was known for only 5 of the 16 patients and it is likely that several of the patients had no significant hepatic disease and merely isolated elevations in their enzymes. However, the improvements in liver enzymes were seen in all but 1 of the patients who received IDN-6556, suggesting that the drug may have a broader hepatoprotective effect than was originally thought. No decreases in the transaminase levels occurred in the normal volunteers, suggesting that the relationship between transaminase leakage from normal hepatocytes and apoptosis may occur by a different mechanism.

The pattern of decreases in transaminases was similar for the different doses of IDN-6556. Discernable reductions were typically seen by the second day after dosing. Near maximal reductions appeared to have developed by Day 5 of dosing, although future studies will be needed to evaluate if further changes will occur with more than 1 week of dosing. Although there were no statistically significant differences in the transaminases before treatment, the levels were not identical. This observation, together with the obvious fact that the patient numbers at each dose of drug were small, suggest that it is inappropriate to make definitive statements about the dose-response relationship of the drug from this study.

When the drug administration was stopped, the transaminase values typically returned to baseline levels within 3 days. In a few individuals (in the 0.1 and 0.5 mg/kg dosing groups), their transaminases exceeded their baseline and screening values, typically reaching a maximum level 1 – 7 days after the drug was stopped, before returning to pre-treatment levels 14 days after drug cessation. The highest post-treatment value occurred in a patient who received 0.5 mg/kg and is shown in Figure 4. Although the rebound enzyme levels in this study were not of clinical concern, this phenomenon needs to be evaluated in future trials and consideration has been given to utilizing tapering regimens to blunt the effects of withdrawal of drug therapy. Both the onset and post-treatment rebound effects seen in this study are consistent with the effects of a drug that is inhibiting apoptosis and, after it is withdrawn, allows the resumption of cell death in 2 cohorts of cells (those whose death were inhibited during drug treatment and a new cohort whose death started after the drug was stopped).

This study indicates that further clinical evaluation with IDN-6556 is merited. There

is a clear clinical need for better therapies for many hepatic diseases in which apoptosis has been implicated, including viral hepatitides, alcoholic hepatitis and ischemia-reperfusion injury associated with liver transplantation. Clinical data are needed to answer the many questions about the potential clinical utility and safety issues of anti-apoptotic drugs; however, this study raises the possibility that IDN-6556 may prove to be clinically useful. The role and potential for anti-apoptotic therapy remains to be defined.

## Conclusion

This Phase 1 study of IDN-6556, an irreversible caspase inhibitor that prevents apoptosis, is believed to be the first clinical trial for a compound of its class. The observations from the safety and tolerability and pharmacokinetic endpoints in hepatic impaired patients were consistent with the experience with single and multiple dosing in normal volunteers.

- IDN-6556 was generally well tolerated in patients with mild elevations of their liver transaminases. Phlebitis was the most significant adverse event.
- Improvements in liver transaminases were seen in patients treated with IDN-6556. The enzyme levels returned to pre-treatment values shortly after drug administration stopped and exceeded pre-treatment values in a few patients.
- One patient showed an elevation in liver transaminases with administration of IDN-6556.
- Pharmacokinetic evaluation was consistent with a drug cleared quickly from the venous circulation after infusion.

## Acknowledgments

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