

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
21-204**

**Medical Review(s)**



---

---

## **Summary**

This safety update is in response to our request for additional information regarding

- 1) Hypoglycemic events
- 2) Dosages in patients with CRI

### **Hypoglycemia**

Data from three studies are presented.

Study 103 compares Satrlix (120-mg/TID) to Metformin. Seventy patients received Satrlix. 7.1% of these patients had symptoms compatible with hypoglycemia. None of these patients required assistance from a third party or discontinued therapy.

Study 116 enrolled ~175 patients per arm (30, 60, 120-mg TID). 163 patients received placebo. ~11% of patients in the lower Satrlix doses experienced hypoglycemia. 22% in the 120-mg dose did. 4% of the patients on placebo experienced hypoglycemia. Plasma glucose levels  $\leq 3.3$  nmol/L were determined in 4, 4, and 6% of patients respectively. In placebo patients it was 2%. A similar trend of discontinuation was seen in the Starlix treated group due to this AE (1%, 1%, 2%) when compared to placebo (0%).

Study B352E02 had 121 patients treated with Satrlix alone (180-mg) and an additional 52 patients treated with a similar Starlix dose plus Metformin. The number of symptomatic hypoglycemia in both arms was ~19%. The number of patients with plasma glucose levels  $\leq 3.3$  nmol/L was 4% for the Starlix alone and 8% on the combination therapy. No patient discontinued the study due to these events.

### **Summary:**

The number and severity of these reports mimic the contents of the original NDA.

### **Renal insufficiency:**

The sponsor correctly states that there is no regulatory requirement to define dosages in special populations. They conducted studies in patients with CRI and their glucose control deteriorated when switched from other antidiabetic drugs. This information is very important establishes a basis not to recommend patients with this underlying condition to be switched to Satrlix. This should be disclosed in the label, because patients switching from other drugs to Starlix could deteriorate their glucose control.

### **Postmarketing:**

No information on postmarketing experience with Satrlix was submitted.

**MEDICAL OFFICER REVIEW**

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)

APPLICATION #: 21704

APPLICATION TYPE: Safety Update

SPONSOR: Novartis

PROPRIETARY NAME: Starlix

CATEGORY OF DRUG: Hypoglycemic Agent

USAN / Established Name: Nateglinide

ROUTE:

MEDICAL REVIEWER: Malozowski

REVIEW DATE: 12/21/00

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/13/00	12/13/00	Safety Update	

**RELATED APPLICATIONS (if applicable)**

Document Date:	APPLICATION Type:	Comments:
----------------	-------------------	-----------

**Overview of Application/Review:** The document covers safety information from the original studies, the open label portion of some of the previously submitted studies. This is a very poorly crafted document that fails to disclose information necessary to make judgments on its contents. Additionally, there is no information on postmarketing AEs that have happened since the 120 day-safety update. Most reports of AEs are blinded and attribution can not be made. The quality of this document does not allow me to render any recommendation. Even if attribution of all listed AEs could be made, the type of reports does not allow to the establishment of pattern different from previous safety reviews. It is quite surprising however, that not a single case of hypoglycemia was included in this document.

**Outstanding Issues:** The Division Director and the Office Director will have to make a judgement on the adequacy of this document to allow this drug to be approved. The submitted material is inadequate to support a positive recommendation.

**Recommended Regulatory Action:**

New Clinical Studies: \_\_\_\_\_ Clinical Hold \_\_\_\_\_ Study May Proceed

NDA's:

Safety update: I cannot recommend any action due to the inadequacy of the submitted document

Signed: Medical Reviewer: Saul Malozowski

Date: 12/15/00

Medical Team Leader: Saul Malozowski

Date: 12/15/00

---

---

## Summary

This safety update summarizes available data for the period from 2/1/00-9/1/00. It covers data on 1387 subjects randomized in 15 clinical studies. Most of the new information replicates what was initially reported in the clinical trials. The many AEs reported in this document could not be clearly attributed to Satrlix because the reports are still blinded. Not a single report of hypoglycemia, the most common AE in the clinical studies and in the 120-day safety update, is recorded in this report. In addition, no laboratory abnormalities were included in this report.

This safety update fails to include reports of AE form postmarketing surveillance.

The quality of this document is so inadequate that it is not possible to render a recommendation.

## Recommendation

I cannot render a positive recommendation from the review of the data enclosed in this document.

## Review

The information provided covers the time period between 2/1/00-9/1/00. It includes data from extension studies, and from pharmacological studies. Some of the clinical studies were in progress at the time of submission and some were terminated.

**A total of 1387 patients were enrolled, 930 completed the studies and 703 were exposed to Satrlix.**

## Exposure

An approximated exposure table is listed below.

	~Number	Duration	30	60	120	180
Study 103	70	16 weeks			70	
Study 116	525	24 weeks	175	175	175	
B351-E-02	121	52 weeks				121

It is important to underline that patients in study 116 were not type 2 diabetics, as defined as having fasting plasma glucose  $\geq 140$  mg/L. The upper limit to be included in this study was 150 mg/L and there is no data to assess how many subjects were below the 140 mg/L limit. Therefore approximately 75% of the safety information in this update does not pertain to the to be approved indication (for patients with type 2 diabetes.) In addition 25% of the studied subjects used a dose (30 mg) that has been shown not to be effective. Inclusion of this data may result in a false sense of safety because the data submitted includes an ineffective dose. Moreover 75% of the subjects that may have slightly elevated FPG not being full blown diabetics may have effective contraregulatory mechanisms that may ameliorate potential bouts of hypoglycemia.

**This data suggest that the patient exposure was ~386 patient year. Of those ~121 patient years were with the 180 mg dose (although only 50% of them finished the 52 week study), ~100 with the 120 mg dose, and the remaining 160 years equally divide between the 60 and 30 mg doses.**

### **Demographics**

No demographic information was included. The lack of this information further complicates any conclusion that could be reached in this review. We do not know the age, the weight, the BMI, the disease progression and other variables that may affect the safety of this product.

### **Adequacy of Safety Testing**

Most of the monitoring was performed in studies and extension studies. This leads me to believe that the data collected during this monitoring phase is adequate.

### **Deaths in clinical studies**

No reports of death were listed in the completed studies.

One case of colon cancer resulting in death one month after the drug was discontinued was reported. The report is still blinded and I do not know what medicine the patient was receiving.

### **Deaths in postmarketing**

No data on postmarketing were enclosed in this document although in excess of subjects were treated until the end of January 2000.

### **Serious AE**

The information provided in this document is inadequate to properly address this section. I will report on what the sponsor submitted.

There are two reports of MI in subjects receiving Satrlix (2.9% of patients with Satrlix) in study 103. The case reports are not identified in the summary document.

In study 116 two patients each had bronchospasm, two angina pectoris and two coronary artery disease (total for each 0.4%). One report of MI in a patient on Satrlix is listed (page036) but not summarized. The case reports are not identified in the summary document. In addition, the sponsor pulled submaximal doses (30) with effective doses (60-120) in this section. The adequacy of this maneuver is questionable.

Attached tables list serious AEs rates in the range of 3.7-11.6% (pages 19-20). The nature of these events is not disclosed nor discussed in the document.

The numbers in these tables also are different to those listed in the summary section. For study 103 the number of randomized patients is 114 not 140 (from where I derived my estimated 70 subjects in the table). The numbers of patients randomized in study 116 is 509 and not what I estimated (~175/group/total 525 without controls). Therefore, the exposure may be much lower than previously estimated. This may provide a false sense of safety because the denominator is indeed smaller and the time exposure shorter.

Additional tables also (post text table 2-1-2, 2-1-3, and 2-1-4) suggests that patients did not completed the trials as designed. It is estimated that 30% of the patients may have dropped out due to lack of efficacy (As per Dr Koller Review). This also underscores the overestimate or patient exposure in this document. Keep in mind that these approximations were calculated based upon information in the summary section of the document. These are not in sink with information listed in other sections.

In addition, in the tables for study B351E02 there are reports including MI, breast cancer, liver disorders, gangrene, cardiac failure, etc., are not summarized. The case reports are not identified in the summary document.

**Discontinuation due to AE**

This is not disclosed in the document.

**AE reports by age**

Not available.

**AE reports by sex**

Not available.

**AE reports by race**

Not available.

**AE by BMI**

Not available.

**AEs' Incidence**

Not available. It is very difficult to assess this because the document is contradictory. In page 13 the sponsor states, that the number of sAEs ( $\geq 1\%$ ) in the placebo group was 3.7% while on Starlix varied between (4.3-8.3%). In the following pages the tables list serious AEs rates in the range of 3.7-11.6% (pages 19-20).

**Hypoglycemia**

This has not been listed in any section of this report although hypoglycemia was identified as the most common AE during the clinical studies.

When Starlix is added to insulin sensitizers, or other antidiabetic drugs, the potential for hypoglycemia may increase. In this report there are studies of Satrlix in combination with Metformin and Rezulin. No cases of hypoglycemia are, however, listed.

**Laboratory**

There are not lab reports in this document.

**Pregnancy**

There are no reports of pregnancy among these studies.

### **Postmarketing reports**

There are not postmarketing reports included in this document.

### **Patient Narratives**

The sponsor has enclosed 95 additional pages with narratives of AE. All reports but one are of patients that remained blinded to study drug at the time of the submission. Therefore, I cannot evaluate these reports and render a valuable comment.

### **Summary**

This document lacks information on the patient demographics, exposure, and fails to connect data reported in the summary section with patients' reports. There are discrepancies in the summary and the attached tables. The number of severe AE appears to be less in the summary than in the tables. There are at least two more MI that are not listed in the summary. In addition there are cancer reports and other serious AE that are not listed.

Moreover the tables fail to properly allow for an estimate of exposure and given the great number of doses used it is difficult to render a conclusion particularly because many of the subjects studied may not had had type 2 diabetes rendering any conclusions questionable; patients with type 2 tend to be more compromised than subjects with pre diabetic conditions.

The lack of hypoglycemic report question the veracity of this document. There are not reports of any abnormality in laboratory values.

Finally, the postmarketing reports form a database that should comprise more than        subjects are missing.

Therefore, I cannot evaluate these reports and render a valuable comment.

### **Recommendations**

The submitted document is grossly inadequate. I cannot render a positive recommendation from the review of the data enclosed in this document.

APPEARS THIS WAY  
ON ORIGINAL

### MEDICAL OFFICER REVIEW

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)  
APPLICATION #: 21204 APPLICATION TYPE: 120 day Safety Update

SPONSOR: Novartis

PROPRIETARY NAME: Starlix

CATEGORY OF DRUG: Hypoglycemic Agent

USAN / Established Name: Nateglinide

ROUTE:

MEDICAL REVIEWER: Malozowski

REVIEW DATE: 12/21/00

#### SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
4/18/00	4/19/00	Safety Update	

#### RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

**Overview of Application/Review:** The document covers safety information from the original studies, the open label portion of some of the previously submitted studies as well as from postmarketing reports collected in Japan.

**Outstanding issues:** There are not outstanding issues that emerge from this safety update.

#### Recommended Regulatory Action:

New Clinical Studies: \_\_\_\_\_ Clinical Hold \_\_\_\_\_ Study May Proceed

NDA:

120 Day Safety Update: XX Approvable \_\_\_\_\_ Not Approvable

Signed: Medical Reviewer: Saul Malozowski Date: 12/11/00

Medical Team Leader: Saul Malozowski Date: 12/11/00

---

---

## Summary

This review summarizes the 120-day safety update submitted by the sponsor. It covers data on 1510 subjects randomized in 14 clinical studies. Most of the new information replicates what was initially reported in the clinical trials. In this context, the most common and expected adverse reaction associated with Satrlix has been hypoglycemia. Other of the many AE reported in this document could not be clearly attributed to Satrlix. This is in part due to the fact that many of these reports are from open label studies, thus the lack of adequate concomitant controls limits the ability of this reviewer to make judgments on the potential association between Satrlix and these events. This should not be construed as a criticism to the sponsor because most safety updates suffer from the same defect.

In addition, this safety update includes reports of AE from postmarketing surveillance. Postmarketing reports may encompass patients that are substantially different in their underlying condition (s) to those required to be included in the supporting clinical studies.

All the enclosed information does suggest that the data emerging from the pivotal studies suffice to make a fair judgement to properly label this compound. No perturbing signals surfaced in these extension studies. Thus, my initial recommendations for the labeling of this product stand except for the expansion on the special populations section a warning that the 60 mg dose should not be used due to lack of efficacy and for the sponsor to clarify whether the 120 dose is effective in these patients.

## Recommendation

Approval with label changes in the renal impairment section.

## Review

The information provided covers the time period between 6/26/99-6/31/00. It includes data from extension studies, from pharmacological studies and Japanese postmarketing experience.

The clinical studies were in progress at the time of submission except for one extension study that was terminated, and another study in renally impaired patients that was closed early.

One of the pharmacological studies is completed and three were ongoing at the time of this submission and all of them were in diabetic patients with type 2. One of the ongoing studies is a multiple dose study while the others were single dose.

A total of 1510 patients were enrolled, 464 of which are discussed in this update received Satrlix. 461 of these has a least one safety evaluation. Most of these patients received the medication in open label studies. Thus the lack of an adequate comparator makes the assessment of this data very difficult.

422/464 subjects were enrolled in an extension study and received the 120-mg dose. Safety reports are available for 405 individuals. This dose was the most commonly used and therefore most of this review addresses issues related to this dose

34 patients participated in a 24-week study in patients with renal impairment that was terminated early (B102-E-00). Patients failed to respond to then 60-mg dose and became hyperglycemic. The sponsor states that this dose *"is especially contraindicated in patients with severe renal impairment due to advance diabetes."*

### **Exposure**

The mean exposure was 23.2 weeks (range [ — ]). 71% of the patients were treated at least for 24 weeks and 46% for more than 6 months. Although the sponsor has not provided adequate information to properly establish the patient-year exposure, I have estimated this to be ~450-550 patient years.

In addition [ — ] subjects have received Satrix in Japan where it has been approved. Data emerging from reports in Japan do not yet suggest a pattern of AE different from those experienced in the supporting clinical studies or in the extension studies. This is reassuring. The marketing experience, however, is limited and the quality of postmarketing reports imperfect.

### **Demographics**

These parameters are similar as those in the original studies. Patients were on average ~60 years and obese (mean BMI ~30). The mean disease progression was also similar as those in the original studies as well as the level of basal HbA1C.

### **Patients disposition**

Seventy percent of patients enrolled (297/422) completed the studies. Thirty percent discontinued early (125/422). Of those 51/122 discontinued due to unsatisfactory control, 42 to "other" causes, 19 to AEs, 10 to protocol violations, two to death and one secondary an abnormal lab test.

### **Adequacy of Safety Testing**

Most of the monitoring was performed in extension studies. Most of the reports are also limited to a single dose (120-mg.) This constrains lead me to believe that the data collected during this monitoring phase is adequate.

### **Deaths in clinical studies**

These reports encompass the clinical studies and the extension studies. Two subjects died during the studies and one 22 days after drug discontinuation

Patient 356E01/055/0021 was a 68 years old male on Satrix for 172 days. The cause of death is listed a accidental asphyxiation secondary to a fall that resulted in loss of conscience. It is difficult to establish a cause relationship of this case with Starlix.

Patient 356E01/020/0017 was a 68 year old male that suffered a MI after 162 days on Satrix. Macrovascular disease and MI is one of the most common causes of death in subjects with diabetes.

Patient 356E01/025/0016 was a 61 male died 22 days after discontinuing Satrix that was received for 197 days. The cause of death is listed a pleural effusion.

None of these cases could be attributed to Satrix. There are case reports for all hypoglycemic agents that resulted in demise of subjects having hypoglycemia and loss of conscience and accidents. In the clinical trials, however, hypoglycemia, and in particular severe hypoglycemia, was extremely rare.

#### **Deaths in postmarketing**

There is one case of death secondary to suicide in one 56 year old female patient after ten days on Starlix. The patient was also receiving several neuroleptics.

#### **Serious AE**

Five percent of the subjects reported at least one serious AE. Except for hypoglycemia that is related to the mechanism of action of Satrix, no other serious AE could be clearly be attributed to this drug.

#### **Discontinuation due to AE**

Five percent of patients were discontinued due to an AE. One third were hypoglycemic episodes. None of these hypoglycemic events were listed as serious. Similar trends were seen in the original medical review. This is reassuring.

#### **AE with $\geq 3\%$**

These reports mimic what has been requested in the AE reports of the original studies. This reports adds hyporeflexia that is not listed in the label.

#### **AE reports by age**

More than 1/3 of the patients in this NDA were  $\geq 65$  years old. The safety profile seems to be quite similar in younger and in older patients. This information could be added to the label.

#### **AE reports by sex**

One third of the subjects were females. The type of AE was similar in males and females but females reported more AE. The reason for this discrepancy is unknown.

#### **AE reports by race**

Approximately 80% of the subjects were Caucasians. Due to the small number of subjects in other races is not possible to make an assessment of whether AE are more common in distinct racial groups.

#### **AE by BMI**

The pattern of AE appears to be similar by BMI. It appears that some reports (hypoglycemia, headache, arthropathy, flu, hypertension, dizziness and diarrhea) were more common in the obese subjects (BMI  $\geq 30$ )

#### **AEs' Incidence**

The sponsor has presented a "crude" incidence of AE. As stated before it is difficult to assess a comparative incidence due to the lack of a concomitant control.

#### **Hypoglycemia**

This was the most frequently reported AE. Most of these reports are characterized as hypoglycemia by a number of signs and symptoms but not by glucose determinations. Of the 16% reports with this term

only 1/3 had concomitant low blood glucose levels. Of the 68 patients reports of symptomatic hypoglycemia six discontinued the studies.

Hypoglycemia was identified as the most common AE during the clinical studies. It was quite rare in the studies. Hypoglycemia was also described during the toxicological studies where animals developed hypoglycemia. Hypoglycemia is expected in a drug that induces insulin secretion and that has been developed to decrease glucose values. The results of the clinical studies suggest that if patients take this medication with meals, as indicated, it would be quite difficult to experience hypoglycemia. The current proposed label clearly states that the medication should be taken only with meals suggesting that a dose should be skipped if a meal is not ingested.

When Starlix is added to insulin sensitizers, or other antidiabetic drugs, the potential for hypoglycemia may increase. This is well known by physicians using antidiabetic drugs and it is properly addressed in the hypoglycemia section in the label.

### **Laboratory**

Reports in this section mimic the pattern of reports in the clinical studies. Uric acid was elevated as it was during the trials. Mean CPK levels were increased in patients receiving Starlix while those in the control group had a decrease from baseline. No other trends were observed in the laboratory values, although reports with alterations of many of these variables are listed in this document. Many of these variables increased and later normalized during the studies.

### **Clinical relevant increases in laboratory values**

#### **Alkaline Phosphatase**

Two subjects had elevated AP. One had concomitant elevations of LFTs. The second was being evaluated for cancer of the pancreas.

#### **CPK**

Four subjects had CPK above 300%. Fluctuations of these values were seen during the studies. No firm cause-effect relationship can be established.

#### **Creatinine**

Two subjects had elevations in creatinine. One normalized the creatinine values while on therapy. The second patient was on multiple medications with an extensive history of cardiovascular disease.

#### **Calcium**

During the extension studies 7 subjects had > 10% increase in total calcium. Despite this elevations the calcium levels were within normal limits. Curiously this shift in Ca levels was 2-3 times that observed in the various treatment groups in the controlled segment of the trial. The clinical significance of these elevations, if any, are unknown.

### **Other laboratory abnormalities**

Laboratory abnormalities encompassing different enzymes and hematological parameters were reported. The number of reports was quite limited and it is not possible to attribute them to Starlix. Patients receiving diabetic medications are complex and may have concomitant diseases and receiving medications that may explain, in part, these derangements. I do not see a pattern in these reports.

### **Pregnancy**

There are no reports of pregnancy among these studies.

### **Postmarketing reports**

Approximately 100 subjects have received Satrlix in Japan in five months after its introduction. In this period, 17 serious and 117 non-serious reports were received by the sponsor. Among the serious the reported death, one case of atrial fibrillation, one of jaundice (in a subject with pre-existing biliary cirrhosis and cancer), three reports of LFTs elevations (one with viral hepatitis and two not yet resolved) three cases of abnormal LFT that improved upon Starlix discontinuation, and a long list of individual cases with other conditions. Other LFTs elevations are listed but not as serious.

Two subjects were discontinued due to rashes and a third patient had a desquamation while on Starlix. The follow-ups are difficult to assess but it appears that the conditions improved with drug discontinuation.

As usual these reports are problematical to evaluate and conclusions of cause and effect relationships difficult to assess.

### **Studies with Rezulin**

The sponsor conducted studies (not reviewed) to assess the comparative efficacy of Rezulin and Starlix. Safety data of the Starlix alone arms were included in this and the original NDA safety review. I have not listed AEs on the combination of these two products. These included AEs currently listed in the approved thiazolidinedione products (weight gain, anemia, and edema.) There were not cases of congestive heart failure.

### **Effects of trial exclusions on safety profile vs expected marketed population and relationship with other drugs available for this indication**

Studies for drug development in patients with diabetes usually exclude subjects with long standing diabetes. These individuals are more prone to develop complications. Currently in the market there are numerous medications with similar mechanism of action that belong to the sulfonylurea class and one drug similar to Satrlix. The AEs that may result due to the pharmacological effect of this drug (i.e. insulin release and secondary hypoglycemia) are similar to all these other drugs. Many of these have been in the market for more than 30 years. The potency of this medication when compared to many of the available sulfonylureas appears to be more modest. Documentation in the NDA suggests that Glyburide, a commonly used antidiabetic drug with a similar mechanism of action, taken once a day results in better glycemic control than Starlix.

Moreover, Satrlix shorter half-life that results in a single insulin peak and its circumscribed efficacy as reflected by its modest ability to induce improvements in HbA1c (most comparative studies were done with submaximal doses of the comparator products) suggest that the potential for hypoglycemia with this product is limited (as shown in the supportive studies.)

Therefore, regarding hypoglycemia this product used alone will probably result in less reports than most of the currently approved drugs. The down side to this desired safety property, is that it provides worst

glycemic control increasing the risks for short and long term complications associated with the underlying condition.

No other AEs emerged from this NDA suggesting that Satrlix may have unique toxic effects. The information collected suggest that this drug appears to be quite safe.

Finally, there are not pending safety issues that need to be resolved except for the inefficacy at the 60 mg dose in patients with CRI and to clarify whether the 120 mg is effective in these patients. The proposed label does not address these issues.

APPEARS THIS WAY  
ON ORIGINAL

**EXECUTIVE SUMMARY: NDA #21204 DJN 608 Nateglinide Starlix**

**Introduction**

The sponsor has developed a modified amino acid analogue of D-phenylalanine because it has long been known that amino acids or mixed meals will still stimulate insulin release from the islet cells when glucose is no longer effective in doing so. The insulin release occurs shortly after drug ingestion so the drug is taken in conjunction with meals. Although this insulin release happens early on, it is not the same as first phase insulin release, which occurs within the first five minutes after beta cell stimulation and is a marker of islet cell health. Nonetheless, the sponsor sought to develop an insulin release profile that would correspond to the absorption of glucose with meals. It was hoped that minimizing glucose in the peri-meal period would be sufficient to mitigate against nocturnal hepatic glucose release and would reduce insulin-glucose mismatch resulting in hypoglycemia.

**Important Pre-clinical Data**

a--The compound is a diol. Diols have the potential to undergo chemical conversion to epoxides. There was, however, no evidence that such conversion occurred or that DJN 608 exhibited adverse events typical of epoxides, e.g. carcinogenesis or teratogenicity.

b--*In vitro* data suggested that glyburide, a commonly used sulfonylurea and insulin secretagogue, was more potent than DJN 608.

c—Some *in vivo* data suggested that neuropathy was more common in female rats treated with the highest doses of DJN 608, but these findings were not replicated in other animal studies. Neuropathic changes were not reported in the clinical trials, but the trials were not structured to assess neuropathy, and, because there are high background rates of neuropathy in diabetics, it is not clear that neuropathic adverse events would have been attributed to the drug.

**Important Pharmacokinetic-pharmacodynamic (PK-PD) Data**

a--The data suggested that the drug was rapidly absorbed with a  $t_{max}$  of approximately one hour and that the drug was short-lived with a  $t_{1/2}$  of approximately 1.5 hours. The glucose lowering effect of the drug paralleled its levels in the serum. An increased  $C_{max}$  level corresponded to an increase in insulin release.

b--There was a peculiar food effect. The optimal time for taking the drug was between one and ten minutes prior to meals. Ingestion without subsequent food intake or ingestion with food altered the drug's absorption. The time to  $C_{max}$  was extended and the  $C_{max}$  was reduced. Total drug exposure, the area-under-the-curve (AUC), was not altered. Liquid dietary intake appeared to alter absorption more than solid dietary intake. The  $C_{max}$  was further reduced,  $t_{max}$  was further delayed, and insulin release appeared to be less. Changes in compounding, including pill packing pressure, did not alter this observation.

c—The studies performed to establish bioequivalence between the formulation used in the phase III trials and the formulation to be used for marketing were not done in the fasted state—as required. They were done in the fed state to reduce PK-PD variability.

d-- The drug is metabolized by the liver. Drug exposure (AUC) was increased by 30% in patients with hepatic disease. There was a 37% increase in  $C_{max}$ , shorter  $t_{1/2}$ , increased renal clearance, and reduced total clearance. These findings cannot be extrapolated to patients with severe disease because significant numbers of patients with such disease were not included in this small and limited pharmacokinetic study.

e--The drug is renally excreted. No differences in AUC and  $C_{max}$  for patients with moderate to severe renal failure were observed. Although there was a 75% reduction in clearance of the parent drug, the presence of more parent drug initially resulted in additional hepatic metabolism and ultimately in less parent drug being available for renal clearance. Patients on hemodialysis experienced a reduction in protein binding of the drug, but the clinical significance of this is unclear because drug exposure was less due to other pharmacokinetic alterations.

f—The drug is a 2C9 inhibitor and is protein bound. No *in vivo* drug interactions were identified. Digoxin, warfarin, and metformin were among the drugs studied. Glyburide and cyclosporin inhibited DJN 608 metabolism *in vitro*. Such findings with glyburide could not be confirmed *in vitro* and may well be related to lower plasma levels of the drug. Comparable *in vivo* studies were not performed with cyclosporin.

### **Important Clinical Data**

The sponsor conducted nine phase II and III clinical trials that are summarized in table 1. A total of 3,164 patients were randomized in the eight completed, double-blind, placebo or active-controlled studies that were eight to 24 weeks in duration. 3,113 patients had efficacy values obtained after the randomization visit. 2,477 patients completed their clinical study. DJN 608 was administered before the three main meals of the day.

**Table 1—Features of the Clinical Trials**

Study	Design	Duration	Randomized, ITT, Drop-Out	Extension, Duration, Comments	Entry, ITT, Drop-Out
202	-- <i>Monotherapy</i> --Dose-ranging (30-180 mg) or placebo --Double-blind* --Parallel design --Patients on diet-exercise after 8 week washout	12 weeks	$N_R=289$ $N_I=288$ $N_D=24$	--Yes, 40 weeks --Double-blind --Open-label metformin could be added	$N_E=227$ $N_I=226$ $N_D=24$
302	-- <i>Monotherapy</i> --DJN dose-ranging (60-180 mg) or placebo --Double-blind* --Parallel design --Patients on diet-exercise after 8 week washout**	24 weeks	$N_R=697$ $N_I=685$ $N_D=134$	No	NA

355	-- <u>Comparative therapy</u> --DJN (120 mg), glyburide (10 mg), or placebo --Double-blind* --Parallel design --Patients on diet alone for 4 weeks prior to week -4 and subsequent 4 weeks	8 weeks	N <sub>R</sub> =152 N <sub>I</sub> =150 N <sub>D</sub> =9	No	NA
304	-- <u>Comparative therapy</u> --DJN (60, 120 mg) or glyburide (10 mg) --Double-blind# --Parallel design --In patients already on (sub) maximal SU therapy --Run-in with glyburide 10 mg for 4 weeks	24 weeks	N <sub>R</sub> =563 N <sub>I</sub> =552 N <sub>D</sub> =226	No	NA
251	-- <u>Add-on therapy to glyburide</u> --DJN (60, 120 mg) or placebo + glyburide (10 mg) --Double-blind --Parallel design --In patients already on SU and then switched to glyburide (10 mg) for 8 weeks	12 weeks	N <sub>R</sub> =172 N <sub>I</sub> =167 N <sub>D</sub> =27	--Yes, 40 weeks --Double-blind --No additional medication permitted. --Could be DCed for hyperglycemia	N <sub>E</sub> =92 N <sub>I</sub> =88 N <sub>D</sub> =53
351	-- <u>Comparative and combination therapy</u> --DJN (120 mg), submaximal metformin (500 mg TID), combo, or placebo --Double-blind* --Parallel design --Patients on diet-exercise after 8 week washout** --Metformin titrated up post randomization	24 weeks	N <sub>R</sub> =701 N <sub>I</sub> =685 N <sub>D</sub> =193	--Yes, 28 weeks --Double-blind --DJN 608 120 mg added to patients on placebo --Open-label metformin could be added	N <sub>E</sub> =400 N <sub>I</sub> =391 N <sub>D</sub> =176
252	-- <u>Add-on therapy to metformin</u> --DJN (60, 120 mg) or placebo +metformin (500 mg TID) --Double-blind --Parallel design --Patients on SU+metformin (≥1500 mg/d) 4 weeks prior to week -4 and on combo therapy ≥8 weeks prior to week -4	12 weeks	N <sub>R</sub> =123 N <sub>I</sub> =123 N <sub>D</sub> =25	Eliminated by amendment	NA
354	-- <u>Add-on therapy to metformin</u> --DJN (60, 120 mg) or placebo + metformin (1g BID) --Double-blind --Parallel design --Patients with prior use of metformin ≥1.5 g/d for ≥4 weeks prior to -4 weeks --Patients received metformin (2 g/d) during 4 week run-in	24 weeks	N <sub>R</sub> =467 N <sub>I</sub> =463 N <sub>D</sub> =49	No	NA
356	-- <u>Comparative and combination therapy</u> --DJN (120 mg), troglitazone (600 mg), combo, or placebo --Double-blind* --Parallel design --Patients on diet-exercise after 8 week washout**	24 weeks; truncated at 16 weeks	N <sub>R</sub> =599 N <sub>I</sub> =585 N <sub>D</sub> =252	No	NA

DJN dosing TID; glyburide dosing qD.

\*Double-blind after randomization; single-blind run-in of DJN. # Double-blind after randomization, single-blind run-in of glyburide.

\*\*Patients were apparently to have stopped any oral hypoglycemic agents 4 weeks prior to the study screening and 8 weeks prior to randomization.

ITT=intent-to treat NR=Number randomized NI=Number with last-observation-carried-forward (LOCF) for-intent-to-treat analysis  
ND=Number who dropped out NA=Not applicable SU=sulfonylurea DCed=discontinued

a--Glycemic control as measured by HgbA<sub>1c</sub> was better with DJN 608 than placebo in three and six month studies. Differences did not exceed 1% in any of the studies.

b--Glycemic control in the trials differed for patients who had previously been on therapy and those who were naïve to medical intervention. Glycemic control was better for the latter. The magnitude of the response, i.e. change in fructosamine or HgbA<sub>1c</sub>, however, was similar for both naïve and non-naïve patients—except in Study 351, where it was less for the non-naïve patients.

c— There were limited clinical differences in the doses of DJN 608. The 30 mg dose was not tested in phase III trials. The 60 mg, 120 mg, and 180 mg doses were tested in a single, 24 week study (Study 302). The combination studies employed the 120 mg dose. In the dose ranging study, drug naïve and non-naïve patients dosed with DJN 60 mg, 120, or 180 mg TID decreased their HgbA<sub>1c</sub> values from baseline by 0.3%, 0.5%, or 0.6% respectively whereas patients treated with placebo increased their HgbA<sub>1c</sub> by 0.2%. 22% of drug-naïve patients dosed with DJN 608 60 mg TID achieved a 1% decrease in HgbA<sub>1c</sub> whereas 30% and 34% of drug-naïve patients dosed with DJN 608 120 and 180 mg TID respectively achieved similar decreases. 25% of drug non-naïve patients dosed with DJN 608 60 mg TID achieved a 1% decrease in HgbA<sub>1c</sub> whereas 31% and 34% of drug non-naïve patients dosed with DJN 608 120 and 180 mg TID respectively achieved similar decreases. There were no profound differences in the level of hypoglycemia (blood glucose  $\leq$ 36 mg/dl and/or requiring intervention) by dose. These minimal differences between the 60 and 120 mg doses were observed also in Studies 251 (add-on to glyburide) and 354 (add-on to metformin)

d—The therapeutic response to DJN 608 did not differ by age or gender.

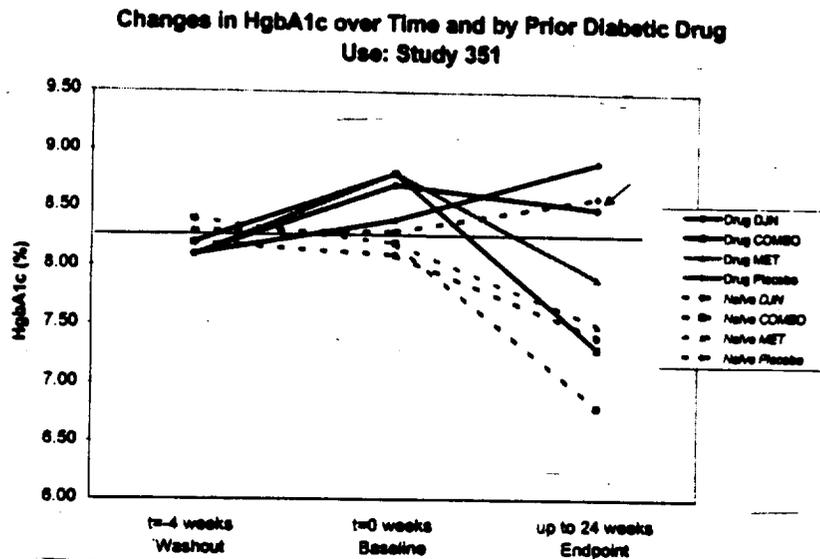
e--Patients who were previously treated with oral hypoglycemic agents, primarily glyburide, experienced deterioration in their glycemic control when they were switched to DJN 608 (Figure 1). In head-to-head studies with DJN 608 and glyburide, glycemic control was better in the patients treated with glyburide. In additive studies, DJN 608 did not improve the glycemic control provided by glyburide--suggesting that the two medications operate through the same receptor mechanisms, K<sub>ATP</sub> channels associated with the sulfonylurea receptor.

f--DJN 608 was less efficacious than submaximal metformin, but could be used in combination with metformin. The effects were additive. More specifically, in naïve patients, metformin (500 mg TID) and DJN (120 mg TID) appeared to have comparable levels of glycemic control. In non-naïve patients, however, metformin lowers glucose more effectively than DJN 608. In both naïve and non-naïve patients, DJN 608 and metformin in combination improves glycemic control better than either agent alone (Figure 1).

Data from Study 354 suggest that is likely that the addition of DJN to the treatment regimen of patients who are incompletely controlled with metformin alone will result in improved glycemic control. Interpretation of the study is limited, however, because it is not known how many patients were on equilibrium doses of near maximal metformin (2 gms/d) at the

time of randomization and because approximately 30% of the randomized patients had already achieved HgbA1c levels below 7%.

Fig. 1



In study 351, patients entered a four week washout before being randomized to one of four treatment arms. Patients who were naïve to diabetic drug therapy did not experience deterioration in glycemic control during the washout period. Patients who had previously been treated with oral hypoglycemic agents, primarily glyburide, experienced deterioration in glycemic control. Non-naïve patients who were treated with DJN 608 improved their glycemic control, but did not reach the level of control at the immediately prior to drug washout. The improvement in glycemic control for non-naïve patients was less in patients treated with DJN 608 alone than that in patients treated with metformin with or without metformin. Although the response in naïve patients tended to parallel the response in non-naïve patients, the response to treatment in the DJN arm was greater in the naïve patients than the non-naïve patients.

g—The utility of DJN with various PPAR agonists is unknown. The study with troglitazone was truncated because of the post-marketing appearance of hepatic problems. This study was not reviewed because its duration was limited, troglitazone is no longer marketed, and there is no class labeling for use of PPAR agonists in combination with insulin secretagogues.

h—The endpoints of post-prandial glucose designated by the sponsor have limited clinical significance. Measures of long-term glycemic control (HgbA<sub>1c</sub> or fructosamine) or the change in such measures over time were poorly correlated with parameters such as the glucose excursion. Although DJN 608 may acutely lower glucose levels more effectively than glyburide, the glucose exposure as measured by the 2 hour AUC<sub>glucose</sub> and the 4 hour AUC<sub>glucose</sub> was the same for the two drugs. Similarly, the 2 hour AUC<sub>glucose</sub> was similar for metformin and DJN 608. This reflected the lower fasting glucose baseline and the sustained glucose lowering observed with glyburide and metformin.

i—The rates of hypoglycemia were low and are consistent with published rates observed in NIDDM patients with comparable levels of glycemic control.

k-- Weight gain was present in patients on DJN 608 or glyburide. Differences could be observed as early as eight weeks. Weight loss was observed in patients on placebo or metformin. Weight gain on combination DJN 608+metformin therapy was intermediate to

that seen with monotherapy with either agent. For the insulin secretagogues, the magnitude of weight gain was proportionate to the improvement in glycemic control. The relationship, however, was indirect.

l--Only limited conclusions could be drawn about long-term efficacy and safety. Drop-out rates exceeded 15% in Studies 302, 304, 251, 351, 252, and 356. Data from Studies 302 and 351 suggested that drop-outs had poorer glycemic control on exit than did patients who completed their study. In addition, only limited numbers of patients entered and completed the three extension trials and rescue therapy with metformin was permitted in two of the studies. Although mean serial HgbA<sub>1c</sub> data suggested stability in glycemic control over time, this stability appeared to have resulted from the serial exclusion of patients with deteriorating HgbA<sub>1c</sub> values.

### **Regulatory Conclusions**

**RECOMMENDATION: APPROVABLE WITH CHANGES IN THE LABEL AND COMPLETION OF THE REQUIRED BIOPHARMACEUTICAL STUDIES AND FINANCIAL DISCLOSURE.**

a--The drug is approvable as monotherapy for naïve patients. Patients who have been on other oral agents, especially currently available insulin secretagogues and metformin, should not be switched because of the expected decline in glycemic control.

b--The drug is approvable in as combination therapy with metformin or as add-on therapy to metformin in either naïve or non-naïve patients.

c-- Physicians must also be advised that long-term efficacy has not been established.

d--There are sufficient clinical efficacy and safety data to support only the 120 mg dose.

e--The phase III clinical tablets must be shown to be bioequivalent to the final marketing image tablets under fasting conditions.

f--The label must delineate the food effects.

g--The post-prandial insulin and glucose parameters have not been validated so these data cannot be used in the label or advertising.

h--The post-marketing adverse event reports suggested that there may be problems in patients with alterations in protein binding or on hemodialysis and in patients on drugs metabolized via cytochrome P450 3A4. These must be addressed in the label and preferably with additional studies.

h--The Sponsor may not infer or state that the drug is safer than other alternatives because of the limitations in the safety data collection.

i-- The Sponsor must provide complete financial disclosure. Data from numerous investigators were not submitted.

- 1. Medical Officer Review
  - 1.1. Administrative Summary
    - 1.1.1. NDA: #21204
    - 1.1.2. Review: #1
    - 1.1.3. Submissions
      - 1.1.3.1. Paper submission: 12/17/99
      - 1.1.3.2. CANDA submission: none
      - 1.1.3.3. Major amendment: none
      - 1.1.3.5. Review completed: 11/11/00
  - 1.2. Drug Name
    - 1.2.1. Generic names: DJN 608; Nateglinide
    - 1.2.2. Proposed trade names: Starlix
  - 1.3. Sponsor: Novartis
  - 1.4. Pharmacologic category: diabetic; insulin secretagogue
  - 1.5. Proposed indications: Dosing TID with meals
  - 1.6. Dosage form and route of administration:
    - 1.6.1. Dosage form: pills: 60 mg, 120 mg, and 180 mg
    - 1.6.2. Dosage: to be titrated
    - 1.6.2. Route of administration: Oral
    - 1.6.3. Combination therapy: glyburide, metformin, or troglitazone
  - 1.7. NDA drug classification: Standard
  - 1.8. Important related drugs: sulfonylureas such as glyburide  
insulin secretagogues such as repaglinide
  - 1.9. Related reviews: IND,                      label
  - 1.10. Materials reviewed: Volumes: 1—3, 138--312
    - NDA #21204 2-24-00 BM Diskette
    - NDA #21204 3-17-00 BM Diskettes
    - NDA #21204 3-31-00 BM Diskette
    - NDA #21204 4-20-00 BM Diskette
    - NDA #21204 6-1-00 BS Protocol copies
    - NDA #21204 6-9-00 BS Electronic data
    - NDA #21204 6-21-00 BS
    - NDA #21204 6-30-00 BS SAS Data
    - NDA #21204 7-6-00 BS SAS Data
    - NDA #21204 7-17-00 BM Diskette
    - NDA #21204 8-16-00 FAX BM/BB
    - NDA #21204 9-21-00 BM Diskettes
    - NDA #21204 10-4-00 BM
    - NDA #21204 10-9-00 FAX regarding information location
    - NDA #21204 10-10-00 BM
    - NDA #21204 10-13-00 BM
    - NDA #21204 10-13-00 FAX regarding t.com.
    - NDA #21204 10-20-00 BB
    - NDA #21204 10-23-00 BM
    - NDA #21204 11-1-00 BM
    - IND                      3-21-00-00 N-161 S2 and 6-21-00 N-177 S3 Dyspnea-interstitial pneumonia
    - IND                      4-4-00 N-163 S2 Reversible renal failure
    - IND                      5-22-00 N-173 S3 New angina and fatal MI
    - IND                      5-25-00 N-174 S2 Dysrhythmia
    - IND                      5-26-00 N-175 S3 Thrombocytopenia
    - IND                      6-28-00 N-179 S3 Abnormal liver function tests
    - IND                      7-5-00 Phone call, 7-12-00 N-180 S2, and 8-16-00 N-185 S3  
Cardio-respiratory arrest and death without hypoglycemia. Concomitant cisipride.

*Administrative*

IND [redacted] 8-25-00 N-187 S2 Asthma/rales  
 IND [redacted] 9-6-00 N-190 S2 Non-hepatic encephalopathy  
 IND [redacted] 7-7-00 N-191 S2 Nocturnal hypoglycemia/subsequent coma in dialysis patient  
 IND [redacted] 9-7-00 N-192 S2 Sudden death after switch from glyburide  
 IND [redacted] 9-12-00 N193 S3 Reversible hypotension without hypoglycemia  
 IND [redacted] 11-1-00 N-206 S2 Possible aplastic anemia

Safety updates: none

1.11. Table of contents	
1. Administrative issues	1
2. Introduction	4
3. Prior agreements	4
4. Objectives	4
5. CANDA	4
6. Financial conflicts	4
7. Chemistry issues	4
7.1. Study drug formulation	4
7.2. Dose-Route-Administration	5
7.3. Other	5
8. Pre-clinical issues	5
9. Pharmacokinetic-pharmacodynamic issues	5
10. Study design	7
10.1. General	7
10.2. Patient selection criteria	7
10.2.1. Inclusion criteria	7
10.2.2. Exclusion criteria	8
10.3. Patient characteristics-Special populations	9
10.4. Safety studies and parameters	9
10.5. Efficacy variables	10
10.6. Statistical analysis	10
10.7. Inspections	11
11. Efficacy results	11
11.1. Compared to placebo	11
11.2. Naïve and non-naïve patients	12
11.3. Dose response	12
11.4. Effect of age	13
11.5. Effect of gender	13
11.6. Efficacy compared to other anti-diabetic agents	13
11.6.1. Glyburide	13
11.6.2. Metformin	13
11.6.3. Troglitazone	14
11.7. Other efficacy parameters	14
11.8. Sustained efficacy	15
12. Safety Results	15
12.1. Deaths	15
12.2. Adverse reactions	16
12.3. Hypoglycemia	17
12.4. Weight gain	17
12.5. Allergic reactions	17
12.6. Neuropathy	18
12.7. Clinical laboratory studies	18

12.8. EKGs	19
12.9. Sustained efficacy	19
13. Commentary	19
14. Regulatory conclusion	21
15. Label review	22
16. Figure legends	48
17. Figures and tables	54
18. Appendices	

APPEARS THIS WAY  
ON ORIGINAL

## **2.--Introduction**

The sponsor has developed a modified amino acid analogue of D-phenylalanine referred to as DJN 608 during development, nateglinide because of its membership in the meglitinide class of drugs, Starlix for anticipated U.S and European marketing, and Fastic or Starsis for its development and current marketing in Japan as 30 and 90 mg tablets. This compound was developed because it has long been known that amino acids or mixed meals will stimulate insulin release from the islet cells when glucose is no longer effective in doing so. The insulin release occurs shortly after drug ingestion so the drug is taken in conjunction with meals. Although this insulin release happens early, it is not the same as first phase insulin release, which occurs in the first five minutes after beta cell stimulation and is a marker of islet cell health. Nonetheless, the sponsor sought to develop an insulin release profile that would correspond to the absorption of glucose with meals. It was hoped that minimizing glucose in the peri-meal period would be sufficient to mitigate against nocturnal hepatic glucose release and would reduce insulin-glucose mismatch resulting in hypoglycemia.

## **3.--Prior agreements**

The sponsor agreed to provide clinical data for medical officer review use on EXCEL files.

## **4.--Objectives**

The sponsor has sought to show that:

- a--This new insulin secretagogue has unique pharmacokinetic and pharmacodynamic properties that result in rapid glucose lowering in the post-prandial period,
- b--DJN 608 provides glycemic control better than placebo, and
- c--DJN 608 can be used in combination with metformin.

## **5.--CANDA**

There was no CANDA submission. Additional data were provided on EXCEL spread sheets.

## **6.--Financial interests**

The sponsor prepared an incomplete financial disclosure report.(Vol.138) There were some investigators who were not available and some who did not return reports [

---

---

---

## **7.--Chemistry issues**

### **7.1--Study drug formulation**

Nateglinide is (-)-N-[(trans-4-isopropylcyclohexyl)carbonyl]-D-phenylalanine with a molecular weight of 317.43. The inactive ingredients include colloidal silicon dioxide, croscamellose sodium, hydroxypropylmethylcellulose, iron oxides (red or yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.

## **7.2.—Dose-Route-Administration**

The sponsor has proposed three doses (60, 120, 180 mg) to be taken orally immediately before meals.

## **7.3.—Other**

The compound is a diol. Diols have the potential to undergo chemical conversion to epoxides. There was, however, no evidence that such conversion occurred or that DJN 608 exhibited adverse events typical of epoxides, e.g. carcinogenesis or teratogenicity.

## **8.—Pre-clinical issues**

### **8.1.—Mechanism and relative potency**

*In vitro* data indicated that the drug was an insulin secretagogue and suggested that glyburide was more potent than DJN 608.

### **8.2.—Toxicology**

#### **8.2.1.—General**

Despite the food effects, drug levels indicated that there was systemic exposure in the animals. The animal data suggested that there were few toxic effects.

#### **8.2.2. Neuropathy**

Some *in vivo* data suggested that neuropathy was more common in female rats treated with the highest doses of DJN 608, but these findings were not replicated in other animal studies. Neuropathic changes were not reported in the clinical trials, but the trials were not structured to assess neuropathy, and, because there are high background rates of neuropathy in diabetics, it is not clear that new neuropathic adverse events would be attributed to the drug.

## **9.—Pharmacokinetic-pharmacodynamic (PK-PD) issues**

### **9.1.—PK-PD properties**

The data suggested that the drug was rapidly absorbed with a  $t_{max}$  of approximately one hour and that the drug was short-lived with a  $t_{1/2}$  of approximately 1.5 hours. The glucose lowering effect of the drug paralleled its levels in the serum. An increased  $C_{max}$  level corresponded to an increase in insulin release.

### **9.2.—Food effect**

There was a peculiar food effect. The optimal time for taking the drug was between one and ten minutes prior to meals. Ingestion without subsequent food intake or ingestion with food altered absorption. The time to  $C_{max}$  was extended and the  $C_{max}$  was reduced. Total drug exposure, area-under-the-curve (AUC), was not altered. Liquid dietary intake appeared to alter absorption more than solid dietary intake. The  $C_{max}$  was further reduced,  $t_{max}$  was further delayed, and insulin release appeared to be less. Changes in compounding, including pill packing pressure, did not alter this observation.

### **9.3.—Bioequivalence between formulations**

The studies performed to establish bioequivalence between the formulation used in the phase III trials and the formulation to be used for marketing were not done in the fasted state—as required. They were done in the fed state to reduce PK-PD variability.

### **9.4.—Hepatic metabolism**

The drug is metabolized by the liver. Drug exposure (AUC) was increased by 30% in patients with hepatic disease. There was a 37% increase in  $C_{max}$ , shorter  $t_{1/2}$ , increased renal clearance, and reduced total clearance. These findings cannot be extrapolated to patients with severe disease because significant numbers of patients with such disease were not included in this small and limited pharmacokinetic study.

It should be noted that there was one post-marketing case from Japan (PHBS2000JP10105) that involved a patient being treated for cirrhosis and hepatic cancer. The patient developed hepato-renal syndrome after being switched from insulin to Fastic. The Fastic was discontinued subsequently, but the patient became febrile and died.

### **9.5.—Renal metabolism**

The drug is renally excreted. No differences in AUC and  $C_{max}$  for patients with moderate to severe renal failure were observed. Although there was a 75% reduction in clearance of parent drug, the presence of more parent drug initially resulted in additional hepatic metabolism and ultimately in less parent drug being available for renal clearance. Patients on hemodialysis experienced a reduction in protein binding of the drug, but the clinical significance of this is unclear because drug exposure was less due to other pharmacokinetic alterations.

It should be noted that a post-marketing clinical report from Japan involving a renal patient switched from acarbose to Fastic (dose unknown) (PHBS2000JP08360) indicated that the patient developed problematic hypoglycemia despite use of corticosteroids and dose reduction of DJN 608. These actual use data suggest that the PK-PD properties of the drug may differ in renal patients dosed on a more extended basis.

### **9.6.—Drug interactions**

The drug is metabolized by cytochrome P450 2C9 (70%) and 3A4 (30%) and is a 2C9 inhibitor. It is also protein bound—especially to albumin, levels of which may be lower in diabetic patients through urinary loss. No *in vivo* drug interactions were identified. Digoxin, warfarin, and metformin were among the drugs studied. Glyburide and cyclosporin inhibited DJN metabolism *in vitro*. Such findings could not be confirmed *in vivo* for glyburide and may well be related to lower plasma levels of drug. Such *in vivo* studies were not performed for cyclosporin.

It should be noted that one post-marketing case of sudden death (PHBS2000JP03816) has been reported in a Japanese patient on Cisipride to whom Fastic was added one day prior. Cisipride has been associated with QT abnormalities, and morbidity and mortality is increased with the concomitant use of medications that are metabolized via the cytochrome

P450 3A4 pathway. Therefore, drug interactions via the cytochrome P450 3A4 system cannot be excluded.

## **10.—Study design for clinical trials**

### **10.1.—General**

The sponsor conducted nine phase II or III studies in support of the NDA. The trials ranged in length from eight weeks to 24 weeks (Table 1). There were three extension trials; two of 40 weeks duration; one of 28 weeks duration. The studies were all parallel-design with patients being blinded to the receipt of DJN 608 or the comparator or the placebo in the treatment phase. The blind was retained for the extension studies—except for the switch of patients in the placebo arm of Study 351 to DJN 608. Add-on medications were also permitted in two of the extension trials. Trials were conducted in the U.S. and abroad, which affected patient composition (Table 2).

### **10.2.—Patient selection criteria**

#### **10.2.1.—Inclusion criteria include:**

**Age:**  $\geq 30$  years: Studies 252, 302, 304, 351, 354, and 356

(upper age limited deleted for study 252)

30—75 years: Studies: 202 and 251

(upper age limit increased for study 251)

30—70 years: Study: 355

**Duration of NIDDM:**  $\geq 3$  months: Studies: 202, 251, 302, 304, 351, 355, and 356

$\geq 6$  months: Study: 354

**BMI:** 20—35 kg/m<sup>2</sup>: Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

**On adequate contraception:** Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

**Screening HgbA<sub>1c</sub>:** 6.8—11% at weeks -8 and -2: Study: 251

6.8—11% at weeks -4 and -2 (may be mean): Studies: 302, 351, 354, 355, and 356

6.8—11% at week -4: Study: 252

6.8—10.5% at weeks -4 and -2: Study: 202

6.5—10% at weeks -4 and -2: Studies: 304

(Amended from 6.8%)

1.5% difference between weeks -8 and -2: Study: 251.

**Fasting plasma glucose (FPG):**  $>140$  mg/dl mean for weeks -4 and -2: Study: 202

$>140$  mg/dl mean for weeks -8 and -2: Study: 251

$\leq 198$  mg/dl at weeks -4 and -2: Study: 252

(Amended from  $\leq 216$  mg/dl at week -4.)

$\geq 90$  mg/dl for mean of weeks -4 and -2: Studies: 252

(Amended from  $\geq 140$  mg/dl.)

**On diabetic diet therapy:** at least 1 month prior to -4 weeks: Studies: 202, 302, 351, 355, and 356

#### **Pharmacologic therapy:**

-Prior treatment with sulfonylureas (SU): glibenclamide-glyburide  $\leq 10$  mg/d, micronized glyburide/glibenclamide  $\leq 6$  mg/d, glipizide  $\leq 10$  mg/d, gliclazide  $\leq 160$  mg/d, chlorpropamide  $\leq 400$  mg/d, tolbutamide  $\leq 2$  g/d, or glimepiride  $\leq 4$  mg/d for at least 12 weeks: Study: 304

-Prior treatment with sulfonylureas and metformin: Study: 252

-Prior treatment with sulfonylurea (dose unspecified)+metformin for at least 8 weeks prior to week -4: Study: 252 (Amended from 12 weeks and a minimum metformin dose.)

-Prior treatment with sulfonylurea (dose unspecified) +metformin  $\geq 1.5$  gm/d for at least four weeks prior to -4 weeks: Study: 252. (Amended from 12 weeks.)

-Prior treatment with glyburide  $\geq 10$  mg/d or glipizide  $\geq 15$  mg/d for at least four weeks prior to week -8: Study: 251

Sustacal challenge response of C-peptide:  $>0.5$  pmol/ml at week -8: Study 251

### 10.2.2.—Exclusion criteria include:

Pregnancy and/or lactation: Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

IDDM or secondary diabetes: Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

Fasting plasma glucose:  $>270$  mg at weeks -4 and -2: Studies: 302, 304, 351, 354, 355, and 356

$>275$  mg/dl at weeks -8 and -2: Studies: 251

$>275$  mg/dl at weeks -4 and -2: Studies: 202

$>198$  at weeks -4 and -2: Studies: 252

(Amended from 216 mg/dl.)

(Amended to permit fasting blood glucose could be substituted for plasma glucose at -4 weeks)

History of complicated diabetes, e.g. DKA or hyperosmolar coma:

Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

Diabetic complications including nephropathy and neuropathy (without clear criteria for autonomic neuropathy and gastroparesis):

Creatinine:  $\geq 1.4$  mg/dl females;  $\geq 1.5$  mg/dl males: Studies 351 and 354

$>1.6$  mg/dl: Study: 252

$>1.8$  mg/dl: Studies: 202 and 251

$\geq 2.0$  mg/dl: Study: 355

$\geq 2.5$  mg/dl: Studies 302, 304, and 356

Congestive heart failure (NY classification 3 or 4): Study: 356

Cardiac problems: MI, cardiac surgery, ventricular fibrillation, ventricular tachycardia in the last six months: Studies: 202, 251, 252, 302, 304, 351, 354, 355, and 356

Orthostatic hypotension: (30 mmHg drop in systolic pressure, 15 mmHg drop in diastolic pressure):

Studies: 202, 251, and 252

Weight change:  $>5\%$  in phase 1 portion of trial: Studies: 202, 251, 302, 304, 351, 354, 355, and 356

$>5\%$  in the month prior to week -8: Studies: 251 and 252

Elevated liver function enzymes:  $>2x$  ULN: Studies: 202, 251, 252, 302, 304, 351, 354, and 355

$>1.5x$  ULN: Studies: 356

(Amended from  $2x$  ULN)

Elevated direct bilirubin:  $>1x$  ULN: Studies: 202 and 251

$>1.3x$  ULN: Studies: 302, 304, 351, 354, 355, and 356

Abnormal hepatic serologies: Studies: 202, 251, and 252

(Core antigen for hepatitis-B deleted by amendment: Studies: 202, 251, and 252)

Elevated triglycerides:  $>622$  mg/dl within last 12 week before entry:

Studies: 302, 304, 351, 354, 355, and 356

$>450$  mg/dl persistently: Studies: 202, 251, 252

Use of medication: Oral hypoglycemic agents within 1 month of -4 weeks:

Studies: 302, 351, 355, and 356

Oral hypoglycemic agents within 2 months of -4 weeks: Study: 202

Oral hypoglycemic agents other than metformin within 12 weeks of -4 weeks:  
Studies: 354

Metformin, glitazones, alpha glucosidase inhibitors within 12 weeks of -4 weeks:  
Study: 304

Warfarin: Studies: 202, 251, 252, 302, 304, 354, and 355  
(exclusion amended in study 351)

Digoxin: Studies: 202 and 251 (also initially Study: 252) not 354

Non-selective beta blockers: Studies: 202 and 251 (also initially Study 252) not 354

Oral corticosteroids: Studies: 251, 252, 302, 304, 351, 354, 355, and 356

Cholestyramine: Study: 356

Oral contraceptives: Study: 356

Chronic insulin within last 6 months:

Studies: 202, 251, 252, 302, 304, 351, 354, 355, 356

(Thyroid hormone could be used to achieve a euthyroid state: Studies: 202, 251, 252, 302, 304, 351, 354, and 356.)

### 10.3.—Patient Characteristics—Special Populations

Male patients out-numbered female patients in all studies (Table 3). Less than 10% of patients were from minority groups (Table 3). Most of the patients middle-aged to elderly and were not new diabetics (Table 3). Although many of the patients were overweight, this was not uniformly true (Table 3).

No special population groups were studied.

### 10.4.—Safety studies and parameters

Visits were conducted at least each four weeks after randomization in studies 202, 251, 252, and 356. Visits were conducted at four week intervals after randomization except between weeks 16 and 24 in studies 302, 304, 351, and 354 when the visit interval was longer. Visits were conducted between one and three weeks in study 355. In studies 202, 251, 252, 302, 304, 351, 354, 355, and 356, patients were assessed with a physical exam (including a limited fundoscopic exam and limited assessment of diabetic neuropathy—vibratory sense), vital signs taken while resting and seated (no orthostatic readings), laboratory studies, and an EKG. In addition to endpoint laboratory studies, the laboratory studies included a CBC, routine clinical chemistries, urinalysis dipstick testing, and a TSH value. (The TSH testing was done only at screening/entry for some of the studies.) Patients were given education about hypoglycemia and home glucose monitoring with a glucometer. The meters were to be used in the event of hypoglycemic symptoms and sometimes to obtain serial glucose values for a diurnal profile (Vol. 274, pp. 902, 910).

Glucose meter readings of <50 mg/dl were defined to be hypoglycemic by the Sponsor for studies 202, 251, 252, 302, 304, 351, 354, 355, and 356. Hypoglycemic-like episodes were classified by the Sponsor on the basis of symptoms in studies 202, 251, 252, 302, 304, 351, 354, 355, or 356. Those events with adrenergic symptoms were defined as class 1, those with neurologic symptoms as class 2, those with coma or requiring third-party assistance as class 3, or those requiring hospitalization as class 4.

Patients could be discontinued for hypoglycemia and hyperglycemia. Such hypoglycemia included unexplained class 3 or class 4 episodes or more than three episodes/week in which the blood glucose was <50 mg/dl or serum glucose was <60 mg/dl (in studies 252, 302, 304, 351, 354, 355, 356, but not 202, 251). Such hyperglycemia was defined as symptoms consistent with hyperglycemia, e.g. weight loss, polydipsia, or polyuria, or repeated fasting plasma glucose >270 mg/dl without intercurrent illness in studies 252, 302, 304, 351, 354, 355, and 356. In studies 202, 251, excessive fasting plasma glucose was defined as 275 mg/dl. Patients in the metformin studies were to be monitored for lactic acidosis on an as-needed basis and were to be discontinued for levels  $\geq 5$  mmol/l (studies 351 and 354). In the 202 extension study, the placebo group was maintained as was the blind. Patients with a HgbA<sub>1c</sub> >8.5% or a decrease in HgbA<sub>1c</sub> from baseline of <0.7% could receive metformin, 500 mg TID titrated over three weeks. In the 251 extension study.

patients could not receive any additional medication, but could be discontinued for a HgbA<sub>1c</sub> >10%, an increase in HgbA<sub>1c</sub> from baseline of 1.5%, or a fasting plasma glucose of  $\geq 275$  mg/dl. In the 351 extension study, patients could be discontinued for HgbA<sub>1c</sub> values >10% at 32 weeks and beyond. To facilitate glycemic control, medication could be added to patient regimens. In the extension for study 202, open-label metformin could be added. In the extension for study 351, DJN 608 120 mg TID was added to the treatment regimens of patients on placebo during the randomized portion of the trial. In the same extension study, patients with inadequate glycemic control (fasting glucose >166 mg/dl or HgbA<sub>1c</sub> >7.2%) on DJN 608 could have open-label metformin added to their regimen.

### 10.5.—Efficacy variables

**HgbA<sub>1c</sub>-primary:** Studies: 202+extension, 251+extension, 252, 302, 304, 351+extension, 354, and 356  
(Baseline HgbA<sub>1c</sub>=mean of values from -2 and 0 weeks: Studies: 202, 251, 302, 304, 351, 354, and 356)

**Fructosamine-secondary:** Studies: 202, 251, 302, and 355

**Fasting glucose-primary:** Studies: 202+extension, 251+extension, and 252

secondary: Studies 302, 304, 351+extension, 354, 355, and 356

(Baseline glucose=mean of values from -2 and 0 weeks: Studies: 251, 252, 302, 304, 351, and 354, but not 356)

**Fasting lipids-secondary:** Studies: 202+extension, 251+extension, 252, 302, 304, 351, 354, 355, and 356

**Sustacal challenge PK-PD parameters-primary:** over 4 hours: Study: 355

secondary: over 2 hours: Study: 351

over 4 hours: Studies: 202, 251, and 252

**Body weight-secondary:** Studies: 302, 304, 351+extension, 354, 355, and 356, but not 202, 251, 252

**Waist and hip girth-secondary:** Study: 356

**Lp(a)-secondary:** Study: 356

### 10.6.—Statistical analysis

The studies were to be conducted with a double-blind. Efficacy was to be assessed using the primary efficacy value(s) and the change in the efficacy variable(s) in intent-to-treat (ITT) populations. Baseline values were to be the average of weeks -2 and 0. ANOVA or ANCOVA analyses were to be used. An interim data evaluation was conducted in Study 202 at eight weeks and after patients completed the controlled portion of the trial, but before the extension phase was complete. The statistical reviewer assessed Studies 202, 302, and 304 using an ANCOVA model and found no interaction between treatment and country versus HgbA<sub>1c</sub> or fasting plasma glucose. The medical reviewer defined the ITT population as randomized patients who had an efficacy value beyond baseline. Patients who had no values beyond baseline were excluded. Baseline was defined as t=0 because patients were frequently not at equilibrium during the washout or run-in period that preceded randomization. The medical reviewer compared efficacy values for DJN 608 doses to efficacy values for placebo or comparator treatments using the student t-test. Correlation coefficients were calculated for unvalidated secondary endpoints proposed for inclusion in the label as well as for validated endpoints. It was also recognized that the blind may have been incomplete because patients had blood glucose monitors and would be able to monitor differences in glucose at the time of study entry, during washout, and addition of therapy. For this reason and because such meters are inaccurate, hypoglycemia was more strictly defined as requiring intervention from a third party and/or having a blood glucose  $\leq 36$  mg/dl (2 mmol/L).

The reference ranges for HgbA<sub>1c</sub> were the same for all studies: normal 4—6%.

The reference ranges for fructosamine varied by study and laboratory:

Study 202: SKBL normal 200—278 umol/dl

Study 302: SKBL normal 200—278 umol/dl; Medinet ULN 285 umol/dl

Study 355: unspecified normal 150—320 umol/dl

(Per Mr Schlotfeldt 11/6/00 and Vol. 306 of ISS.)

### 10.7.—Inspections

Inspections were conducted at three sites. There were no problems at the site of Dr. Demidova in Moscow, Russia. There were minor problems at the site

, Germany. Incomplete consent and approval was obtained for the protocol modifications. There were more significant problems at the site

U.S.A. Approval for the study was incomplete. The investigator included patients that should have been excluded on the basis of excessive body mass indices, elevated FSH levels, use of prior oral hypoglycemic agents during the washout period, and elevated ALT measurements. Eight of ten patients had visits conducted outside the protocol time frame. The Sponsor was not notified about a case of severe diverticulosis requiring hospitalization until six months after its occurrence. Records were inadequate in many cases. Patient records indicate discrepancies in the records that would have precluded study entry for three patients. Records for one patient did not include dyesthesia and neuropathic pain documented elsewhere. Drug disposition records were incomplete.

Nevertheless, the conclusions of the studies will not likely be altered by exclusion of data from these two sites.

### 11.—Efficacy results

#### 11.1.—Comparison to placebo

Glycemic control as measured by HgbA<sub>1c</sub> was better with DJN 608 than placebo in three and six month studies. Differences did not exceed 1%. (See tables 4 and 6 from representative study 302 [dose ranging versus placebo] and 351 [DJN 608 120 mg TID versus placebo versus metformin]. See figure 1.) Glycemic control as measured by fructosamine was better than placebo in the eight week study 355 and the 24 week study 302 (Tables 4 and 5). Differences did not exceed 50 umol/dl. Changes in fructosamine paralleled changes in HgbA<sub>1c</sub> although fructosamine measures protein glycosylation over a 10 to 14 day interval rather than hemoglobin glycosylation over three months.

The correlation coefficients for fructosamine versus HgbA<sub>1c</sub> ranged from 0.54 to 0.84 for the various treatment groups in Study 302 (Table 11) There were similar findings for the change in fructosamine versus the change in HgbA<sub>1c</sub>. The correlation coefficient for fructosamine at time of randomization (t=0) and HgbA<sub>1c</sub> at t=-2 weeks in patients who had not been previously exposed to anti-diabetic drugs and who would not be expected to experience significant deterioration in glycemic control during the washout period was 0.59 in Study 355 (Table 12). These data confirmed the relationship between these two measures of integrated or long-term glycemic control and support the premise that glucose control with DJN 608 is better than on placebo alone—although the magnitude of that difference is small.

### **11.2.—Comparison of patients naïve to anti-diabetic drug therapy and patients with prior exposure**

Glycemic control in the trials differed for patients who had previously been on therapy and those who were naïve to medical intervention. Glycemic control was better for the latter. Differences between the two groups for HgbA<sub>1c</sub> ranged from 0.3 to 1.2% for Studies 302 and 351 (Tables 4 and 6). Differences between the two groups for fructosamine ranged from 10 to 19 umol/dl for Studies 302 and 355 (Tables 4 and 5). The magnitude of the response, i.e., change in fructosamine or HgbA<sub>1c</sub>, however, was similar for both naïve and non-naïve patients except in Study 351, in which the response by non-naïve patients was less than the response for naïve patients (Tables 4, 5, and 6)

Mean endpoint values for HgbA<sub>1c</sub> were less than 8% and 9% for patients treated with DJN 608 and placebo respectively (Tables 4 and 6). Mean endpoint values for fructosamine were less than 300 umol/dl and 350 umol/dl respectively for patients treated with DJN 608 and placebo (Tables 4 and 5). These values suggested that most patients had mild to moderately impaired levels of glycemic control. The inclusion of naïve to non-naïve patients in ratios ranging from 2:1 to 5:1 helped to keep these endpoint values lower than it would have been with the inclusion of a higher percentage of non-naïve patients (Tables 4, 5, and 6).

### **11.3.—Dose response**

There were limited clinical differences in the doses of DJN 608. The 30 mg dose was not tested in phase III trials. The 60 mg, 120 mg, and 180 mg doses were tested in a single, 24 week, phase III trial (Study 302) (Table 4). The combination studies employed the 120 mg dose. In the dose ranging study, drug naïve and non-naïve patients dosed with DJN 60 mg, 120, or 180 mg TID decreased their HgbA<sub>1c</sub> values from baseline by 0.3%, 0.5%, or 0.6% respectively whereas patients treated with placebo increased their HgbA<sub>1c</sub> by 0.2% (Figure 2). 22% of drug naïve patients dosed with DJN 608 60 mg TID achieved a 1% decrease in HgbA<sub>1c</sub> whereas 30% and 34% of drug naïve patients dosed with DJN 608 120 and 180 mg TID respectively achieved a similar decrease. 25% of drug non-naïve patients dosed with DJN 608 60 mg TID achieved a 1% decrease in HgbA<sub>1c</sub> whereas 31% and 34% of drug non-naïve patients dosed with DJN 608 120 and 180 mg TID respectively achieved a similar decrease. There were no profound differences in the level of hypoglycemia (blood glucose  $\leq$  36 mg/dl and/or requiring intervention) by dose (Table 4). These minimal differences between the 60 and 120 mg doses were observed also in Studies 251 (add-on to glyburide) and 354 (add-on to metformin)(Figures 5 and 7).

Limited data suggested that patients with higher body mass indices (BMI) might benefit from the 180 mg dose—although obese patients who were diabetic drug-naïve appeared to benefit more than obese, non-naïve patients (Figure 3). (See statistical review.) These data could be consistent with the fact that the volume-of-distribution of this drug is known to be larger in patients with larger BMIs. Such an increase in the volume-of-distribution would require a higher dose to achieve serum drug levels comparable to patients with smaller volumes-of-distribution.

#### **11.4.—Effect of age on efficacy**

The therapeutic response to DJN 608 did not differ by age. HgbA<sub>1c</sub> values at endpoint and the change in HgbA<sub>1c</sub> were similar for patients who were younger than 65 years of age or 65 years of age and older in Study 302 (Table 7). The correlation coefficients for age and change in HgbA<sub>1c</sub> were small, which also suggested the absence of a relationship between age and glycemic control (Table 7).

#### **11.5.—Effect of gender on efficacy.**

More male patients than female patients were randomized in studies with DJN 608 (Table 3). Drop-out rate, although high in many of the studies, did not appear to differ by gender. Nor did the therapeutic response to DJN 608 differ by gender (Table 8).

#### **11.6.—Efficacy compared to other anti-diabetic agents and as add-on therapy**

##### **11.6.1.—Glyburide**

Patients who were previously treated with oral hypoglycemic agents, primarily glyburide, experienced deterioration in their glycemic control when they were placed on DJN 608. This could be seen with serial HgbA<sub>1c</sub> values during washout periods that preceded randomization and after randomization to the DJN 608 120 mg TID cohort (Figure 6). In head-to-head studies with DJN 608 and glyburide, glycemic control was better in the patients treated with glyburide. Endpoint values of fructosamine were lower for patients treated with glyburide than DJN 608 despite higher values for the former at entry to Study 355 (Table 5). The change in fructosamine lowering was three to four times greater for glyburide than for DJN 608 (Table 5). Endpoint values for fasting plasma glucose, as well as the change in fasting glucose during Study 355, were higher for DJN 608 than glyburide despite higher values for the former at entry (Figure 4). In additive studies, DJN 608 did not improve the glycemic control provided by glyburide—suggesting that the two medications operate through the same receptor mechanisms, i.e., K<sub>ATP</sub> channels associated with the sulfonylurea receptor (Figure 5).

##### **11.6.2.—Metformin**

DJN 608 was less efficacious than submaximal metformin, but could be used in combination with metformin (Table 6, Figure 6). The effects were additive. More specifically, in naïve patients, metformin (500 mg TID) and DJN (120 mg TID) appeared to have comparable levels of glycemic control. In non-naïve patients, however, metformin lowered glucose more effectively than DJN 608. In both naïve and non-naïve patients, DJN 608 and metformin in combination improved glycemic control better than either agent alone.

It is likely that the addition of DJN to the treatment regimen of patients who are incompletely controlled with metformin alone will result in improved glycemic control (Figure 7). Interpretation of Study 354 was limited, however, because it was not known how many patients were on equilibrium doses of near maximal metformin (2 gms/d) at the time of randomization and because approximately 30% of the randomized patients had already achieved HgbA<sub>1c</sub> levels below 7%. The addition of DJN 608 to patients, all of whom had not clearly failed metformin, resulted in a decrease of HgbA<sub>1c</sub> levels for both completers and any patient with a follow-up value. When serial HgbA<sub>1c</sub> values were plotted for only the patients

who had a HgbA<sub>1c</sub> ≥7% at the time of randomization (t=0), the values were higher, but the trends for glycemic control over time for this subset of patients appeared to be comparable to the those found in the population-at-large for Study 354 (Figure 8).

### 11.6.3.--Troglitazone

The utility of DJN with various PPAR agonists remains unknown. The study with troglitazone was truncated because of the post-marketing appearance of hepatic problems. The submitted study was not reviewed because its duration was limited, troglitazone is no longer marketed, and there is no class labeling for use of PPAR agonists in combination with insulin secretagogues.

### 11.7.--Other efficacy parameters

The Sponsor proposed the use of multiple post-prandial endpoints, including the glucose excursion, 2 hour post-prandial glucose, and the post-prandial area-under-the-curve (AUC) adjusted to exclude glucose exposure below the baseline (or fasting glucose level), to define superiority for DJN 608. The endpoints of post-prandial glucose designated by the Sponsor have limited clinical significance (Tables 9 and 10). As has been established in prior clinical studies, measures of long-term glycemic control (HgbA<sub>1c</sub> or fructosamine) correlated with fasting glucose levels (Tables 11, 12, and 13, Figure 9). Similarly, changes in HgbA<sub>1c</sub> correlated with changes in fasting glucose. For example, both fructosamine and fasting glucose levels were lowered by glyburide and DJN 608. Furthermore, the magnitude of lowering for both of these parameters was greater for patients treated with glyburide than for patients treated with DJN 608 in Study 355 (Figure 9). Similarly, parallel changes in both fructosamine and fasting glucose levels from Study 302 delineated the limited dose response relationship for DJN 608 (Table 4). By contrast, measures of long-term glycemic control or the change in such measures over time were poorly correlated with the glucose excursion (2 hour post-prandial glucose level minus the fasting glucose level) (Tables 12 and 13). Although the glucose excursion was smaller for DJN 608 than that observed with glyburide, fructosamine lowering was greater for glyburide (Figure 10). Similarly, although the glucose excursion was smaller for DJN 608 than that observed with metformin, HgbA<sub>1c</sub> values at endpoint and the change in HgbA<sub>1c</sub> over the duration of the study were better for metformin than for DJN 608 (Table 10, Figure 11). Although DJN 608 acutely lowered glucose levels more effectively than glyburide, the glucose exposure as measured by the unadjusted 2-hour-AUC<sub>glucose</sub> and the 4-hour-AUC<sub>glucose</sub> was the same for the two drugs (Figure 12). Indeed glyburide was associated with lower fasting glucose, fructosamine, and HgbA<sub>1c</sub> values than DJN 608. This suggests that the magnitude of glucose lowering and the duration of this glucose lowering after treatment with DJN 608 was insufficient to lower the fasting glucose as effectively as glyburide. Similarly, although DJN 608 acutely lowered serum glucose more effectively than metformin, the glucose exposure as measured by the unadjusted 2-hour-AUC<sub>glucose</sub> was the same for these two drugs as well (Figure 13). Although the AUC<sub>glucose</sub> could be correlated to HgbA<sub>1c</sub>, the time interval used and the pharmacokinetic-pharmacodynamic properties of the particular drug will impact the degree of correlation. This may explain the limited correlation between 4-hour-AUC<sub>glucose</sub> and fructosamine observed with glyburide 10 mg given once daily and the higher degree of correlation

between 4 hour-AUC<sub>glucose</sub> and fructosamine observed with DJN 608 given three times daily (Table 12).

### 11.8.—Sustained efficacy

Only limited conclusions could be drawn about long-term efficacy and safety. Although the number of patient-years of exposure exceeded 900, the drop-out rates exceeded 15% in Studies 302, 304, 251, 351, 252, and 356. Data from Studies 302 and 351 suggested that drop-outs had poorer glycemic control on exit than did patients who completed their study (Tables 4 and 6). In addition, only limited numbers of patients entered and completed the three extension trials, and, lastly, rescue therapy with metformin was permitted in two of the studies (Table 1). Although mean serial HgbA<sub>1c</sub> data initially suggested stability in glycemic control over time (Figures 5 and 16), this stability appeared to have resulted from the serial exclusion of patients with deteriorating HgbA<sub>1c</sub> values (Figures 14 through 18, Tables 14 and 15). The deterioration over time became evident when serial data for individual patients and for cohorts of patients classified by the time of their drop-out were plotted.

### 12.—Safety results

#### 12.1.—Deaths

No excess mortality could be attributed to the drug.

a--There was one patient (Study 352 Patient 1010) who died of metastatic lung cancer shortly after completion of an eight week pharmacology trial.

b--There were three patients who died during placebo controlled trials:

Study 302	Patient 0320007	MI and V tach	after 18 days of DJN 608 (120 mg)
Study 202	Patient 0100003	MI	after 31 days of DJN 608 (30 mg)
Study 351	Patient 0100020	Pancreatic CA	first hospitalized after 17 weeks of metformin (500 mg) died 6 months later

c--There were three patients who died after the placebo controlled trials:

Study 302	Patient 0140003	hepatitis A/hepatic failure	presented 39 days post study on placebo died post transplant
Study 351	Patient 0170005	MI	presented at 21 weeks of DJN 608 (120 mg) with aortic stenosis died 1 day post study completion
Study 351	Patient 0910008	CAHD	reported 15 weeks post study completion on metformin (500 mg)

d--There were six patients who died during active controlled trials:

Study 304	Patient 0180017	car accident	after 47 days of DJN 608 (120 mg)
Study 354	Patient 0300010	sudden death	after ?? days of DJN 608 (120 mg)+ metformin (500 mg)
Study 354	Patient 0320006	cardiac arrest	after 110 days of DJN 608 (120 mg)+ metformin (500 mg)
Study 304	Patient 0420015	MI	after 31 days of glyburide (10 mg)
Study 304	Patient 0360006	MI	after 84 days of glyburide (10 mg)
Study 304	Patient 0080003	MI	after 129 days of glyburide (10 mg)

e--There were no deaths in the long-term extension trials.

## **12.2. Adverse events**

### **12.2.1. Adverse events during the clinical trials**

There were 151 reported serious adverse events during the controlled clinical trials (Table 16). The occurrence of these events appeared to be similar for the various treatment groups—although the highest proportion of such events were in the DJN+glyburide combination group. The most common of these serious events were cardio-vascular in nature. The type of adverse event did not differ by treatment group except for the category “aggravation of diabetes”. The three patients in this category were all in the DJN 608 alone treatment group, which represented 43% of the patients exposed in clinical trials (Study 356 excluded) (Vol.302, pp. 93-2 of ISS).

There were 201 adverse events that resulted in discontinuation from the study—although not all of these events were “serious”. The occurrence of these events appeared to be similar for the various treatment groups—although the highest proportion of such events were in the DJN+glyburide combination group as above (Table 16).

The adverse effect profile did not appear to differ by gender or age (Vol. 302, pp.77-78 of ISS). Gastrointestinal symptoms (abdominal pain, diarrhea, dyspepsia, or nausea) were somewhat more common in blacks with DJN 608 alone or in combination with metformin (Vol. 302, p. 80 of ISS). The relatively small number of blacks (<10% of population) may limit any conclusions.

### **12.2.2 Notable adverse events from post-marketing reports (not covered elsewhere)**

Serious adverse event reports have been received from Japan, where the drug is marketed for under two years. There are insufficient numbers of reports to draw definitive conclusions at this time, but the serious nature of the event, the timing of the event, or the response to discontinuation of the drug suggest that such events warrant scrutiny during post-market drug surveillance.

J/00/00047/DJN A 75 year old man developed life-threatening thrombocytopenia 14 days after the initiation of Fastic (270 mg-regimen unknown) and three days after initiation of PL granules, cefdinir, loxoprofen, and serrapeptase for an upper respiratory infection. The thrombocytopenia reversed after discontinuation of medications and institution of corticosteroid therapy. There is no currently available information on whether the patient was rechallenged. Thrombocytopenia has been reported with sulfonylureas and cefdinir.

J/00/00167/DJN A 44 year old man developed a dysrhythmia six weeks after being started on Starsis and three weeks after being fully titrated. Starsis was discontinued, but the patient developed dyspnea. In the subsequent evaluation, the patient was found to have both supra- and ventricular dysrhythmias. The patient was treated with an unspecified anti-arrhythmic agent and switched to gliclazide. Treatment with ethyl icosapentate was continued. The dysrhythmias resolved. AV-block (Stokes-Adams Syndrome) (J000071DJN) and atrial fibrillation (J9900443DJN) have been reported in other patients.

PHBS2000JP04510 A 69 year old man developed hypotension while on Fastic. There was no hypoglycemia or cardiac ischemia. The hypotension improved with discontinuation of the drug.

J/00/00149/DJN A 77 year old woman who had been angina free, developed chest pain, two weeks after initiation of therapy with Starsis and celiprolol. She subsequently died of myocardial infarction and multi-system organ failure.

PHBS2000JP08439 A 77 year old woman with adequate glycemic control on glyburide was switched to DJN 608. Blood pressure control was somewhat inadequate, 130/94. Three weeks after starting DJN, she died acutely with premonitory headache and nausea.

J/00/00173/DJN A 43 year old man developed urticaria and hepatotoxicity three weeks after the initiation of Fastic. Hepatic enzyme and bilirubin levels dropped after discontinuation of Fastic, Pravastatin, and voglibose.

PHBS2000JP08339 A 76 year old woman developed non-hepatic encephalopathy with apraxia and asterixis two weeks after starting Starsis.

J/00/000119/DJN) An 82 year old woman developed elevations in creatinine, BUN, and uric acid 2.5 months after starting on Fastic (270 mg—unknown dosing regimen). These abnormalities resolved after discontinuation of Fastic.

### **12.3.—Hypoglycemia**

The rates of hypoglycemia<sup>1</sup> were low and are consistent with rates found in NIDDM patients with comparable levels of glycemic control (Tables 4, 5, and 6).

<sup>1</sup> For the purposes of this review, hypoglycemia was defined as requiring intervention from a third party and/or having a blood glucose  $\leq 36$  mg/dl (2 mmol/L). This definition is relatively specific for clinically significant events and minimizes problems due to the relative inaccuracy of the home glucose meters and the potential for unblinding in the trials. (See the minutes of the and the 1996 Winter and 1998 Spring E & M Advisory Committee meetings.)

### **12.4.—Weight gain**

Weight gain was present in patients on DJN 608 or glyburide (Figures 19, 20, and 21, Tables 4, 5, and 6). Similar weight gain occurred in naïve and non-naïve patients (Figures 19 and 20). Differences could be observed as early as eight weeks (Figure 21). Weight loss was observed in patients on placebo or metformin (Figure 22, Table 6). Weight gain on combination DJN 608 + metformin therapy was intermediate to that seen with monotherapy with either agent. For the insulin secretagogues, the magnitude of weight gain was proportionate to the improvement in glycemic control (Figure 21, Table 5). Low correlation coefficients indicated that the relationship between weight and glycemic control, however, was indirect.

### **12.5.—Allergic reactions**

Although the frequency of rash in each treatment category was proportionate to the numbers of patients in each category in the clinical trials, the cases of urticaria (2) appear to be limited to patients in the DJN 608 treatment group. Both patients were discontinued from the study. (There was an additional case of angioedema in a patient who presented 26 days after randomization. Because the patient had two similar episodes prior to being started on DJN 608 and after being started on Prinivil, the cause was attributed to the latter. Nonetheless, the patient was switched to amlodipine and discontinued from the study. These patient management responses limit interpretation of the case.)

There has been one post-marketing report (J/00/00173/DJN) in which a 43 year old man developed urticaria and hepatotoxicity three weeks after the initiation of Fastic. Hepatic enzyme and bilirubin levels dropped after discontinuation of Fastic, Pravastatin, and voglibose.

## 12.6. Neuropathy

Extensive neuropathy exams were not uniformly conducted so no comments could be made regarding the clinical significance of the neuropathy findings in rodents.

## 12.7.—Clinical laboratory studies

Laboratory studies including routine clinical chemistry studies, CPK, and a CBC were obtained for patient assessment.

a-- There were increases in mean uric acid levels for patients for patients treated with DJN 608 alone and in combination with metformin. The respective differences from placebo were 17.1 umol/l and 26.9 umol/l. These differences persisted during extension studies. The magnitude of the change for DJN+ metformin combination therapy suggested that the effects of the two drugs were comparable and additive. The percent of patients with a >50% increase in uric acid (umol/l) was similar for the three treatment groups (DJN, metformin, and combination), albeit higher than that of placebo, suggesting that the mean increases were not due to a few outliers with large changes.

These increased levels of uric acid were not associated with more episodes of gout, but increased levels of uric acid have been correlated with increased cardio-vascular morbidity in some epidemiologic studies.

b--There was a mean increase in creatinine in DJN 608 treated patients over placebo treated patients (+1.4 umol/l). The mean increase was somewhat less in the DJN+metformin treated patients compared to placebo treated patients (0.6 umol/l). Similar findings were observed in the glyburide treatment groups, but not in the metformin treatment groups. The number of outliers with a 50% increase in creatinine, however, did not differ by treatment group.

The changes in creatinine likely represent a functional change in renal function and not a drug interaction with the chemical assay for creatinine. In most patients on insulin secretagogues, these changes appear to be small, but as suggested by a post-marketing report from Japan (J/00/000119/DJN), these reversible changes may be more significant in select individuals. An 82 year old woman patient with previously normal renal function presented with elevations in creatinine, BUN, and uric acid 2.5 months after initiation of Fastic therapy (270 mg—unknown dosing regimen). Her anti-hypertensive regimen was replaced, and cerivastatin was discontinued. Her renal function continued to decline: creatinine 2.1 mg/dl, BUN 64.2 mg/dl, and uric acid 11.7 mg/dl. Three days after discontinuation of Fastic, her creatinine dropped to 1.5 mg/dl. Nine days after discontinuation, her creatinine levels were 1.3 mg/dl.

c--DJN 608 had only limited effects on lipids. No mean changes were observed for LDL, but 2.2% of DJN treated patients, 2.4% of glyburide treated patients, and 0.9% of placebo treated patients experienced a >50% increase in LDL (mmol/l).

d--There were no clear differences in the group means, frequency of patients with >200% increase or frequency of outliers >2x ULN for hepatic enzymes (AST, ALT, and GGT [U/L]) by treatment.

The post-marketing report J/00/00173/DJN suggests that hepatotoxicity might be associated with DJN 608 drug use, but the clinical data suggest that this would be a relatively uncommon phenomenon, if true. In this particular case, a 43 year old man developed urticaria and hepatotoxicity three weeks after the initiation of Fastic. Hepatic enzyme and bilirubin levels dropped after discontinuation of Fastic, Pravastatin, and voglibose.

e--There were no clear differences in the group means, frequency of patients with >100% increase or frequency of outliers >2x ULN for alkaline phosphatase by treatment.

f--There were no clear differences in the group means or frequency of patients with >100% increase for total bilirubin by treatment.

g--There were no clear differences in the group means or frequency of patients with >300% increase for CPK by treatment.

h--Slight increases in mean hemoglobin and hematocrit occurred in patients treated with DJN (0.09 gm/dl hemoglobin and 0.2% in hematocrit) and placebo (0.09 gm/dl hemoglobin and 0.4% in hematocrit). It was not known whether these increases were the result of dehydration-diuresis from poor glycemic control or due to another phenomenon.

There was a single, preliminary post-marketing report of possible aplastic anemia with recovery after drug discontinuation (PHBS2000JP10256). It was not clear whether a bone marrow biopsy was done

### **12.8.--EKGs**

No definitive conclusions about the EKG data could be drawn because, although the Sponsor reported that there were no differences in the proportion of patients with new or worsened EKGs by treatment group, there were no criteria delineating "clinically insignificant changes" from "clinically significant changes".(See Vol. 307, pp.1992-1993.)

### **12.9.--Sustained efficacy and long-term safety from extension studies (See Efficacy Section.)**

### **13.--Reviewer's commentary**

DJN 608 is an insulin secretagogue which provides glycemic control that is statistically better than that observed in placebo-treated patients. The glycemic control is inferior to that obtained by glyburide (10 mg/d)<sup>1</sup>. There may be several reasons for this:

a--*In vitro* studies, suggest that it may be intrinsically less potent than glyburide as an insulin secretagogue.

b--The drug has a short half-life and a concomitant short interval of glucose lowering. Because of these pharmacokinetic and pharmacodynamic properties, the drug is unable to provide sustained glycemic control. The fasting glucose levels suggest that patients experience escape from glycemic control in the late post-prandial period and overnight.

c—Because of these pharmacokinetic and pharmacodynamic properties, the drug must be taken with meals. In other words, the drug must be used at least three times per day. Such frequent usage may limit compliance. Unfortunately, escape from glycemic control will occur more readily with missed doses of DJN 608 than with longer acting insulin secretagogues. Indeed, this phenomenon has been observed with short-acting insulin analogues too. Such escapes from glycemic control may contribute to increased insulin resistance—making subsequent return to glycemic control more difficult.

d—The drug has an unusual food interaction. For optimal efficacy, the drug must be taken during a very narrow time window before the ingestion of a meal. In addition, meal composition alters the drug levels and subsequent glycemic response. It is unlikely that patients were able to optimally take the drug three times per day for six months and even less likely that patients were able to adhere to such a regimen for 12 months or longer.

The sponsor is unlikely to be able to improve response rates by increasing the dose. Both animal and human studies suggest that there is a dosing plateau with smaller fractions of subjects with poor glycemic control being captured with each sequential dose increase. Furthermore, the complexities of taking the drug properly three times per day may account for the drop-out over time as well as the deterioration in glycemic control over time.

The drug offers no clear advantage over currently available sulfonylureas—except that it is unlikely to result in the skin reactions associated with sulfa drugs and their derivatives. It should be noted, however, that urticaria has been reported with DJN 608. The rapid glucose lowering as expressed by the glycemic excursion does not predict the level of glycemic control. Indeed, rapid glucose lowering may be physiologically unimportant because protein glycosylation, a mediator for chronic complications, does not occur over minutes. Rather, it occurs over hours and days. Although the glycemic excursion for DJN 608 is less than that observed with glyburide, DJN 608 is less effective than glyburide for the reduction of HgbA<sub>1c</sub>. DJN 608 is likely to be as potent as acetohexamide or tolinaise. In addition, since weight gain and hypoglycemia are more related to levels of glycemic control than the intrinsic structure of an insulin secretagogue, no claims of superiority can be made for DJN 608 over glyburide. Because of the drug's limited potency, patients who have been on other oral agents, particularly second generation sulfonylureas, will likely experience a deterioration in glycemic control. Although the drug can be used successfully in naïve patients and although the drug can be used in combination therapy with metformin, it is likely that economic considerations will determine utilization. For patients who are incompletely controlled by DJN 608, clinicians will likely switch to generic glyburide rather than adding non-generic metformin to a sub-potent DJN 608.

<sup>1</sup> The maximal permitted dose for glyburide in the U.S. is 10 mg BID. Some investigators would say that the 10 mg/d dose used in the DJN studies was submaximal. Limited evidence suggests that a small percentage of a patient population can be captured with an increase to 15 or 20 mg/d. Nathan DM, Roussel A, Godin IF. *Glyburide or insulin for metabolic control in NIDDM*. Annals Intern Med. 1988;108:334-340. See medical officer review IND # — 5-17-97.

**14.--Regulatory conclusions**

**RECOMMENDATION: APPROVABLE WITH CHANGES IN THE LABEL AND COMPLETION OF THE REQUIRED BIOPHARMACEUTICAL STUDIES AND FINANCIAL DISCLOSURE.**

a--The drug is approvable for naïve patients, but patients who have been on other oral agents, especially currently available insulin secretagogues and metformin, should not be switched because of the expected decline in glycemic control.

b--Physicians must also be advised that long-term efficacy has not been established.

c--There are sufficient clinical efficacy data to support only the 120 mg dose

d--The phase III clinical tablets must be shown to be bioequivalent to the final marketing image tablets under fasting conditions.

e--The label must delineate the food effects.

f--The Sponsor has not validated the post-prandial insulin and glucose parameters so these cannot be used in the label or advertising.

g--The post-marketing adverse event reports suggest that there may be problems in patients with alterations in protein binding or on hemodialysis and in patients on drugs metabolized via cytochrome P450 3A4. These must be addressed in the label and preferably with additional studies.

h--The Sponsor may not infer or state that the drug is safer than other alternatives because of the limitations in the safety data collection.

i-- The Sponsor must provide complete financial disclosure. Data from numerous investigators were not submitted.

**APPEARS THIS WAY  
ON ORIGINAL**

26 pages redacted from this section of  
the approval package consisted of draft labeling

## **16.—Serial table and figure legends**

### **Table 1**

The sponsor conducted nine phase II or III studies during the evaluation of DJN 608. The study design, the duration of the study, the character of the patient population, and whether an extension study was conducted are delineated.

### **Table 2**

The number of study sites by country are delineated. The high proportion of non-U.S. study sites contributed to the low number of patients from minority groups.

### **Table 3**

Demographic data for patients randomized into the nine phase II or III trials are summarized.

### **Table 4**

Changes in the parameters of glycemic control are outlined for patients who received placebo and patients who received varying doses of DJN 608 in a 24 week trial. The changes in fructosamine are included along with the changes in HgbA<sub>1c</sub>, the standard measure of glycemic control employed in clinical trials, because fructosamine alone was employed by the Sponsor in Study 355 and such a comparison provides a frame of reference for evaluating glycemic control data in Study 355. The outcomes for patients who were not previously exposed to anti-diabetic drug therapy, i.e., naïve are contrasted with the outcomes for patients who had been previously exposed, i.e., non-naïve because better glycemic control was present in naïve patients. Outcomes for patients who completed the study are contrasted with the outcomes for patients who did not complete the study because drop-out rates after randomization exceeded 20%. Parameters of glycemic control are contrasted with the safety parameters, weight and hypoglycemia, because prior clinical data indicate that they are typically inversely related.

### **Table 5**

Changes in parameters of glycemic control are outlined for patients who received placebo, DJN 608 (120 mg TID), or glyburide (10 mg/d) in an eight week trial. Fructosamine was employed as a measure of long-term glycemic control because the study was not long enough for complete equilibration of HgbA<sub>1c</sub>. The outcomes for patients who were not previously exposed to anti-diabetic drug therapy, i.e., naïve are contrasted with the outcomes for patients who had been previously exposed, i.e., non-naïve. Parameters of glycemic control are contrasted with the safety parameters, weight and hypoglycemia, because prior clinical data indicate that they are typically inversely related.

### **Table 6**

Changes in HgbA<sub>1c</sub> are outlined for patients who received placebo, DJN 608 (120 mg TID) alone, metformin (500 mg TID) alone, or DJN 608 in conjunction with metformin in a 24 week trial. The outcomes for patients who were not previously exposed to anti-diabetic drug therapy, i.e., naïve are contrasted with the outcomes for patients who had been previously exposed, i.e., non-naïve. Outcomes for patients who completed the study are contrasted with

the outcomes for patients who did not complete the study because drop-out rates after randomization exceed 25%. Parameters of glycemic control are contrasted with the safety parameters, weight and hypoglycemia, because prior clinical data indicate that they are typically inversely related.

#### Figure 1

In a dose-ranging study, the sponsor has shown that treatment with DJN 608 resulted in glycemic control that differed from that of patients treated with placebo alone. The magnitude of the difference in HgbA<sub>1c</sub> from placebo did not exceed 1% for the treatment cohorts. Sub-group analysis showed that glucose lowering was similar for naïve and non-naïve patients although the level of glycemic control was poorer for non-naïve patients.

#### Figure 2

In a dose ranging study, the sponsor has shown that there is a trend towards a dose response, but the differences in the proportion of treated patients who are able to decrease their HgbA<sub>1c</sub> level by 1% are small. An increase in the DJN dose from 60 mg TID to 180 mg TID resulted in the capture of an additional 10 % of the patient population. This limited the clinical significance of any dose differences.

#### Figure 3

Patients higher body mass indices (BMI in mg/m<sup>2</sup>) were less responsive to the lower doses DJN 608 than were their thinner counter-parts. This finding is not unexpected because of the proportionate increase in insulin resistance with obesity. The response of patients with higher BMIs was improved with the 180 mg dose. This response was most prominent in the naïve patients who comprised approximately 80% of the 180 mg dose cohort.

#### Table 7

HgbA<sub>1c</sub> and changes in HgbA<sub>1c</sub> were assessed in patients older than 65 years of age and their younger counterparts. Geriatric patients constituted approximately one third of the patient population in Study 302. A greater proportion of older patients had previously taken another anti-diabetic drug. Nonetheless, there were no differences by age in the response to DJN 608.

#### Table 8

HgbA<sub>1c</sub> and changes in HgbA<sub>1c</sub> were assessed in male and patients. Female patients constituted approximately one third of the patient population in Study 302. This imbalance was present in the other studies as well. Nonetheless, there were no differences by gender in the response to DJN 608. There was a trend towards statistical significance that suggested that men had a better response to the 60 mg dose than did women, but the opposite trend was found in the cohort receiving the 180 mg dose—suggesting that these are spurious differences.

#### Figure 4

Fasting plasma glucose was the only parameter of glycemic control measured serially throughout the study period and the prior washout period. No clinically significant changes

in fasting glucose were seen in the diabetic drug naïve patients during the washout. In contrast, deterioration of fasting glucose was observed in the non-naïve patients. The DJN 608 treated patients experienced a decrease in fasting glucose that differed from placebo treated patients, but this decrease was markedly less than the decrease observed in patients treated with glyburide. Although fasting glucose levels were higher in non-naïve patients than in naïve patients, the responses to drug therapy for each group paralleled one another.

#### Figure 5

In Study 251, patients already on sulfonylurea therapy were treated with glyburide 10 mg/d during a run-in period. At the time of randomization, patients received add-on therapy with DJN 608 0, 60, or 120 mg TID. The difference in HgbA<sub>1c</sub> values at 12 weeks (arrow) for patients treated with the DJN (120 mg dose)+glyburide versus glyburide alone was only -0.26%. This difference was not statistically significant. Similarly, the difference in the change in HgbA<sub>1c</sub> over 12 weeks for DJN (120 mg dose)+glyburide versus glyburide alone was -0.21%. This difference was not statistically significant either.

Patients in this study could enter a 40 week extension study. 147 patients, as listed in the legend, were eligible for entry. No additional diabetic therapy was permitted during the extension trial. Although the serial HgbA<sub>1c</sub> values suggest that glycemic control remained stable during the extension, these mean values do not delineate the rate of drop-out and the glycemic control of those who dropped out. (See figures 14 and 15.)

#### Figure 6

In study 351, patients entered a four week washout before being randomized to one of four treatment arms. Patients who were naïve to diabetic drug therapy did not experience deterioration in glycemic control during the washout period. Patients who had previously been treated with oral hypoglycemic agents, primarily glyburide, experienced deterioration in glycemic control. Non-naïve patients who were treated with DJN 608 improved their glycemic control, but did not reach the level of control present immediately prior to drug washout (arrow). The improvement in glycemic control for non-naïve patients was less in patients treated with DJN 608 alone than that in patients treated with metformin with or without metformin. Although the response in naïve patients tended to parallel the response in non-naïve patients, the response to treatment in the DJN arm was greater in the naïve patients than the non-naïve patients.

#### Figure 7

Patients in Study 354 were treated with meformin for at least three months, but the dose was increased to at least 2 gm/d in the month prior to baseline so HgbA<sub>1c</sub> values were not equilibrium values. Patients who had HgbA<sub>1c</sub> levels >6.5% were classified as metformin failures and were permitted to enter the add-on study. The addition of DJN 608 improved HgbA<sub>1c</sub> by less than 1%. The improvement in glycemic control was comparable for the two DJN 608 doses.

#### Figure 8

Because most clinicians would not consider HgbA<sub>1c</sub> values <7% to represent failure in glycemic control, the graph in figure 7 was reconstructed using only those patients who had baseline, albeit, non-equilibrium values, that equaled or exceeded 7%. The average level of glycemic control was poorer, but the response to add-on therapy was similar to that observed with the larger population.

#### Table 9

Multiple parameters of glycemic control were delineated for patients in the eight-week-long Study 355. Fructosamine and fasting plasma glucose are more standard assessments of glycemic control. Fructosamine assesses glycemic control over a 10 to 14 day interval. Fasting glucose assesses overnight glycemic control. Post-prandial glucose contributes to overall glucose control, but some of these post-prandial glucose parameters proposed for demonstration of superiority have not been validated for clinical significance. The post-prandial measurements were obtained during a four-hour Sustacal challenge study.

#### Table 10

Multiple parameters of glycemic control were delineated for patients in the 24 week long study 351. HgbA<sub>1c</sub> and fasting plasma glucose are more standard assessments of glycemic control. HgbA<sub>1c</sub> assesses glycemic control over three month interval. Fasting glucose assesses overnight glycemic control. Post-prandial glucose contributes to overall glucose control, but some of these post-prandial glucose parameters proposed for the demonstration of superiority have not been validated for clinical significance. The post-prandial measurements were obtained during a two-hour Sustacal challenge study.

#### Table 11

The correlations between the generally accepted measures of glycemic control are listed for Study 302. There was a positive correlation between HgbA<sub>1c</sub> and fructosamine levels.

#### Table 12

The correlations between fructosamine and some of the proposed post-prandial parameters are listed. The small glucose excursion or rapid glucose lowering effect of DJN 608 has been touted as its important and unique pharmacodynamic feature. The glucose excursion was not correlated to the fructosamine level or the change in fructosamine level. (See appendix 1 for selected graphic depictions of the relationships between fructosamine and such post-prandial parameters.)

#### Table 13

The correlations between HgbA<sub>1c</sub> and some of the proposed post-prandial parameters are listed. The small glucose excursion (or rapid glucose lowering effect) of DJN 608 has been touted as its important and unique pharmacodynamic feature. The glucose excursion was not correlated to the HgbA<sub>1c</sub> level or the change in HgbA<sub>1c</sub> level. (See appendix 2 for selected graphic depictions of the relationships between HgbA<sub>1c</sub> and such post-prandial parameters.)

#### Figure 9

The magnitude of fructosamine and fasting glucose lowering for patients treated with DJN 608 (120 mg TID) was greater than placebo, but less than that observed with glyburide (10 mg/d).

#### Figure 10

The relationship between fructosamine, an accepted measure of semi-chronic glycemic control, and the glucose was explored for patients in Study 355. The magnitude of fructosamine lowering was greater in patients treated with glyburide (10 mg/d) than in patients treated with DJN 608 (120 mg TID) despite the smaller glucose excursion in patients treated with DJN 608. This suggested that the glucose excursion was not predictive of the response to therapy in either naïve or non-naïve patients.

#### Figure 11

The relationship between HgbA<sub>1c</sub> levels, fasting glucose levels, and post-prandial glucose parameters was explored for patients in Study 351. HgbA<sub>1c</sub> levels were lower in patients treated with metformin (500 mg TID) than in patients treated with DJN 608 (120 mg TID) despite the smaller glucose excursion in patients treated with DJN 608. This suggested that the glucose excursion was not predictive of the response to therapy in either naïve or non-naïve patients (arrows).

#### Figure 12

Fructosamine is an integrated measure of glucose exposure. The AUC<sub>glucose</sub> has been proposed as a measure of glucose exposure. Despite the reported rapid glucose lowering effect of DJN 608, the two and four hour AUC<sub>glucose</sub> levels for glyburide and DJN 608 were the same, and the degree of fructosamine lowering was greater for glyburide. This suggested that the AUC<sub>glucose</sub> over these short time intervals could not predict the response to therapy as measured by fructosamine.

#### Figure 13

HgbA<sub>1c</sub> is an integrated measure of glucose exposure. The AUC<sub>glucose</sub> has been proposed as a measure of glucose exposure. Despite the reported rapid glucose lowering effect of DJN 608, the two hour AUC<sub>glucose</sub> levels for metformin and DJN 608 were similar, and the degree of HgbA<sub>1c</sub> lowering was greater for metformin. This suggested that the AUC<sub>glucose</sub> over these short time intervals could not predict the response to therapy as measured by HgbA<sub>1c</sub>.

#### Figure 14

Evaluation of individual patient data from patients treated with DJN 120 mg TID add-on treatment cohort suggested that patients with increasing HgbA<sub>1c</sub> values left the study and that there were only small numbers of patients who completed the study.

#### Figure 15

Cohorts of patients treated with DJN 120 mg TID as add-on therapy were delineated by the time of exit from the study. Although serial mean HgbA<sub>1c</sub> levels depicted by the dashed line appeared to be stable, they were derived from an ever diminishing patient population.

Cohorts with premature study exit had higher HgbA<sub>1c</sub> levels or an increase in HgbA<sub>1c</sub> prior to exit.

#### Table 14

Cohorts of patients in Study 251 were delineated by the time of exit from the study. Although serial mean HgbA<sub>1c</sub> levels appeared to be constant, they were derived from an ever diminishing patient population. Cohorts with premature study exit had higher HgbA<sub>1c</sub> levels or an increase in HgbA<sub>1c</sub> prior to exit.

#### Figure 16

The addition of DJN 608 (120 mg TID) to placebo treated patients at the time of the extension study resulted in a decrease of HgbA<sub>1c</sub> to the levels observed in patients previously treated with DJN 608. Serial mean HgbA<sub>1c</sub> levels initially suggested that glycemic responses to the various treatments could be sustained throughout the duration of the extension study. The numbers of patients with values at 12 weeks as depicted in the figure legend suggest that there would be sufficient numbers of patients to evaluate during the extension. (See figures 18 and 19.)

#### Figure 17

Evaluation of individual patient data from patients treated with DJN 608 in Study 351 suggested that patients with increasing HgbA<sub>1c</sub> values left the study and that there were only small numbers of patients who completed the study.

#### Figure 18

Cohorts of patients treated with DJN 120 mg TID were delineated by the time of exit from the study. Although serial HgbA<sub>1c</sub> levels depicted by the dashed line appeared to be stable, they were derived from an ever diminishing patient population. Cohorts with premature study exit had higher HgbA<sub>1c</sub> levels or an increase in HgbA<sub>1c</sub> prior to exit.

#### Table 15

Cohorts of patients in Study 351 were delineated by the time of exit from the study. Although serial mean HgbA<sub>1c</sub> levels initially appeared to be constant, they were derived from an ever diminishing patient population. Cohorts with premature study exit had higher HgbA<sub>1c</sub> levels or an increase in HgbA<sub>1c</sub> prior to exit.

#### Figure 19

Weight gain is typically found in patients treated with insulin or insulin secretagogues. Weight gains were found in all three DJN 608 treatment groups. Improvements in glycemic control were all three DJN treatment groups. In the naïve patients, there appeared to be a limited dose response and an inverse relationship between the magnitude of HgbA<sub>1c</sub> lowering and the degree of weight gain.

#### Figure 20

Weight gain is typically found in patients treated with insulin or insulin secretagogues. Weight gains were found in all three DJN 608 treatment groups. Improvements in glycemic

control were all three DJN treatment groups. Although there appeared to be an inverse relationship between HgbA<sub>1c</sub> lowering and weight gain, there was no dose response for weight gain in the non-naïve patients. The weight gain in the 120 mg dose cohort may have been a spurious finding that occurred because of the relatively small number of patients in this patient subset.

**Figure 21**

Weight gain is typically found in patients treated with insulin or insulin secretagogues. There appeared to be an inverse relationship between the magnitude of HgbA<sub>1c</sub> lowering and the degree of weight gain for both glyburide and DJN 608.

**Figure 22**

Weight and HgbA<sub>1c</sub> changes for each treatment cohort were assessed during the washout period and during the study. Patients treated with DJN 608 had an improvement in HgbA<sub>1c</sub> at the expense of weight gain. Patients treated with metformin had a greater improvement in HgbA<sub>1c</sub> without weight gain. The weight gain observed with DJN 608 could be ameliorated with an improvement in glycemic control if DJN 608 was used in combination with metformin. Similar changes were observed for both naïve and non-naïve patients.

**Table 16**

Serious adverse events and adverse events that resulted in discontinuation from the study were delineated by frequency of occurrence in each of the treatment regimens.

**/S/**

Elizabeth Koller, M.D.

**MEDICAL OFFICER REVIEW**

**TABLES**

**APPENDICES**

**FIGURES AND CHARTS**

**APPEARS THIS WAY  
ON ORIGINAL**

Table 1  
Features of Phase II and III Studies for DJN 608

Study	Design	Duration	Screened, Randomized, Gender Race ITT, Drop-Out	Extension, Duration, Comments	Entry, ITT, Drop-Out
202	<p><u>--Monotherapy</u>  --Dose-ranging (30—180 mg) or placebo  --Double-blind*  --Parallel design  --Patients on diet-exercise after 8 week washout</p>	12 weeks	<p>N<sub>s</sub>=516    N<sub>r</sub>=289  M=193 F=96  C=268 B=6  A=1 O=14    N<sub>i</sub>=288    N<sub>d</sub>=24</p>	<p>--Yes, 40 weeks  --Double-blind  --Open-label metformin (500 mg TID) could be added if HgbA1c &gt;8.5% or a HgbA1c decrease from baseline &lt;0.7%</p>	<p>N<sub>e</sub>=227    N<sub>i</sub>=226    N<sub>d</sub>=24</p>
302	<p><u>--Monotherapy</u>  --DJN dose-ranging (60-180 mg) or placebo  --Double-blind*  --Parallel design  --Patients on diet-exercise after 8 week washout**</p>	24 weeks	<p>N<sub>s</sub>=1238    N<sub>r</sub>=697  M=410 F=287  C=609 B=39  A=8 O=41    N<sub>i</sub>=685    N<sub>d</sub>=134</p>	No	NA
355	<p><u>--Comparative therapy</u>  --DJN (120 mg), glyburide (10 mg), or placebo  --Double-blind*  --Parallel design  --Patients on diet alone for 4 weeks prior to week -4  --Patients continued with diet alone for next 4 weeks.</p>	8 weeks	<p>N<sub>s</sub>=378    N<sub>r</sub>=152  M=83 F=69  C=102 B=14  A=3 O=33    N<sub>i</sub>=150    N<sub>d</sub>=9</p>	No	NA
304	<p><u>--Comparative therapy</u>  --DJN (60, 120 mg) or glyburide (10 mg)  --Double-blind#  --Parallel design  --In patients already treated with (sub) maximal SU therapy  --Run-in with glyburide 10 mg for 4 weeks</p>	24 weeks	<p>N<sub>s</sub>=844    N<sub>r</sub>=563  M=359 F=204  C=501 B=18  A=7 O=37    N<sub>i</sub>=552    N<sub>d</sub>=226</p>	No	NA
251	<p><u>--Add-on therapy to glyburide</u>  --DJN (60, 120 mg) or placebo + glyburide (10 mg)  --Double-blind  --Parallel design  --In patients already on SU and then switched to glyburide for 8 weeks</p>	12 weeks	<p>N<sub>s</sub>=348    N<sub>r</sub>=172  M=125 F=47,  C=113 B=9  A=13 O=37    N<sub>i</sub>=167    N<sub>d</sub>=27</p>	<p>--Yes, 40 weeks  --Double-blind  --No additional medication permitted.  --Could be DCed for FPG&gt;275 mg/dl, HgbA1c &gt;10%, or increase in HgbA1c &gt;1.5%</p>	<p>N<sub>e</sub>=92    N<sub>i</sub>=88    N<sub>d</sub>=53</p>

351	<p><b>--Comparative and combination therapy</b>  --DJN (120 mg), submaximal metformin (500 mg TID), combo, or placebo  --Double-blind*  --Parallel design  --Patients on diet-exercise after 8 week washout**  --Metformin titrated up over 3 weeks after randomization</p>	24 weeks	<p>N<sub>s</sub>=1451  N<sub>r</sub>=701  M=436 F=265  C=565 B=83  A=IT O=42  N<sub>i</sub>=685  N<sub>d</sub>=193</p>	<p>--Yes, 28 weeks  --Double-blind  --DJN 608 120 mg added to patients on placebo  --Open-label metformin could be added if FPG&gt;166 or HgbA1c &gt;7.2# (by amendment)  --Exclusion if HgbA1c &gt;10% at 32 weeks &amp; beyond.</p>	<p>N<sub>e</sub>=400  N<sub>i</sub>=391  ND=176</p>
352	<p><b>--Add-on therapy to metformin</b>  --DJN (60, 120 mg) or placebo + metformin (500 mg TID)  --Double-blind  --Parallel design  --Patients on SU+metformin (≥1.5 g/d) 4 weeks prior to week -4 and on combo therapy at least 8 weeks prior to week -4; washout DCed bc of glucose rise</p>	12 weeks	<p>N<sub>s</sub>=243  N<sub>r</sub>=123  M=81 F=42,  C=115 B=5  A=3 O=0  N<sub>i</sub>=123  N<sub>d</sub>=25</p>	Eliminated by amendment	NA
354	<p><b>--Add-on therapy to metformin</b>  --DJN (60, 120 mg) or placebo + metformin (1 g BID)  --Double-blind  --Parallel design  --Patients with prior use of metformin ≥1.5 g/d for at least 4 week prior to -4 weeks;  --Patients received metformin 2 g/d during 4 week run-in</p>	24 weeks	<p>N<sub>s</sub>=680  N<sub>r</sub>=467  M=277 F=190  C=424 B=18  A=14 O=11  N<sub>i</sub>=463  N<sub>d</sub>=49</p>	No	NA
356	<p><b>--Comparative and combination therapy</b>  --DJN (120 mg), troglitazone 600 mg, combo, or placebo  --Double-blind*  --Parallel design  --Patients on diet-exercise after 8 week washout**</p>	24 weeks; truncated at 16 weeks	<p>N<sub>s</sub>=1320  N<sub>r</sub>=599  M=362 F=237  C=474 B=40  A=7 O=78  N<sub>i</sub>=585  N<sub>d</sub>=252</p>	No	NA

Doses of DJN 608 given TID; doses of glyburide given qD.

\*Double-blind after randomization; single-blind run-in of DJN.

# Double-blind after randomization, single-blind run-in of glyburide.

\*\*Patients were apparently to have stopped any oral hypoglycemic agents 4 weeks prior to the study screening and 8 weeks prior to randomization.

ITT=intent-to treat NS=Number screened NR=Number randomized NI=Number with last observation carried forward (LOCF) for intent-to-treat analysis ND=Number who dropped out

M=male F=female C=Caucasian B=Black A=Asian O=Other

NA=Not applicable SU=sulfonylurea Dced=discontinued FPG=Fasting plasma glucose

Table 2  
Location of study sites by country

Location	Study								
	202	251	252	302	304	351	354	355	356
<b>Total</b>	31	14	31	64	70	94	73	22	89
U.S.	6 (North America)	14 (North America)	0	32	15	87	10	22	89
Canada	See above.	See above.	0	5	5	0	2	0	0
Austria	1	0	0	0	3	0	3	0	0
Belgium	0	0	0	0	0	0	1	0	0
Finland	1	0	0	2	0	0	0	0	0
France	2	0	0	3	0	0	0	0	0
Germany	12	0	0	11	16	0	13	0	0
Ireland	0	0	2	0	0	0	0	0	0
Italy	0	0	0	0	8	0	0	0	0
Netherlands	4	0	0	0	1	0	1	0	0
Norway	2	0	0	1	0	0	2	0	0
Poland	0	0	0	4	0	0	0	0	0
Spain	0	0	0	0	0	0	5	0	0
Sweden	1	0	0	0	4	0	2	0	0
Switzerland	0	0	0	3	0	0	2	0	0
UK	2	0	29	0	5	7	5	0	0
Australia	0	0	0	0	8	0	0	0	0
Russia	0	0	0	3	0	0	0	0	0
South Africa	0	0	0	0	5	0	5	0	0

APPEARS THIS WAY  
ON ORIGINAL

**Table 3**  
**Patient Demographics**

<b>Study</b>	<b>Gender % male</b>	<b>Race % Caucasian</b>	<b>Age (yrs) Mean (Range)</b>	<b>BMI (kg/m2) Mean (Range)</b>	<b>Duration of Diabetes (yrs) Mean (Range)</b>
202	67	93	56 (31--75)	29	4.6
302	59	87	58 (31--83)	29	4.6
355	55	67	56 (32--75)	30	5.0
304	64	89	61 (29--85)	28	7.6
251	73	66	57 (33--74)	29	7.9
351	62	81	58 (29--88)	30	4.6
252	66	94	61 (36--83)	29	8.6
354	59	91	57 (30--84)	29	6.8
356	60	79	58 (31--86)	30	4.9

BMI=body mass index

APPEARS THIS WAY  
ON ORIGINAL

# BEST POSSIBLE COPY

Table 4  
Efficacy Compared to Associated Safety Parameters: Study 302

	HbA1c (%)			Fructosamine (µmol/L)			Fasting Glucose (mg/dL)			Weight			# Events During Study				
	t=0 Wks	Exit	Delta	t=0 Wks	Exit	Delta	t=0 Wks	Exit	Delta	t=0 Wks	Exit	Delta					
<b>Placebo</b>																	
<b>LOCF</b>	<b>9.55</b>	<b>26</b>	<b>9.15</b>	<b>26</b>	<b>0.63</b>	<b>24</b>	<b>269.4</b>	<b>262.4</b>	<b>26.4</b>	<b>269.2</b>	<b>264.0</b>	<b>7.0</b>	<b>26.0</b>	<b>0.02</b>	<b>0</b>		
completer	8.24	12	8.80	12	0.56	12				89.44	13	88.68	13	-0.76	13		
non-completer	8.71	22	9.33	23	0.67	12				85.14	24	84.59	24	-0.55	24		
no LOCF	9.55	2								0							
<b>LOCF</b>	<b>7.88</b>	<b>128</b>	<b>7.83</b>	<b>128</b>	<b>0.08</b>	<b>128</b>	<b>218.7</b>	<b>231.7</b>	<b>14.4</b>	<b>222.7</b>	<b>171.50</b>	<b>8.0</b>	<b>128</b>	<b>84.80</b>	<b>128</b>	<b>-0.09</b>	<b>128</b>
completer	7.76	114	7.72	115	-0.04	114				85.33	119	84.70	119	-0.63	119		
non-completer	8.69	15	9.56	15	0.97	15				87.49	14	86.54	14	-0.95	14		
no LOCF	8.28	8								84.82	8						
<b>DJN-60 mg</b>																	
<b>LOCF</b>	<b>8.28</b>	<b>28</b>	<b>8.08</b>	<b>28</b>	<b>0.20</b>	<b>28</b>	<b>208.4</b>	<b>208.8</b>	<b>0.05</b>	<b>208.8</b>	<b>199.80</b>	<b>1.0</b>	<b>28</b>	<b>85.11</b>	<b>28</b>	<b>0.23</b>	<b>28</b>
completer	8.19	32	7.95	32	-0.24	32				85.90	33	85.44	33	0.54	33		
non-completer	8.51	8	8.20	8	-0.31	8				84.78	8	85.44	8	0.66	8		
no LOCF	8.87	3								79.50	2						
<b>LOCF</b>	<b>7.80</b>	<b>117</b>	<b>7.62</b>	<b>117</b>	<b>-0.28</b>	<b>117</b>	<b>208.4</b>	<b>208.8</b>	<b>0.05</b>	<b>208.8</b>	<b>199.80</b>	<b>1.0</b>	<b>117</b>	<b>83.11</b>	<b>117</b>	<b>0.23</b>	<b>117</b>
completer	7.74	115	7.42	115	-0.32	115				82.97	117	83.20	117	0.23	113		
non-completer	8.43	12	8.47	12	0.03	12				80.95	11	81.14	11	0.19	11		
no LOCF	8.45	4								86.97	3						
DJN vs Placebo p=	N.S.		<0.001		<0.001		N.S.		<0.001		<0.001		N.S.		<0.001		
<b>DJN-120 mg</b>																	
<b>LOCF</b>	<b>8.34</b>	<b>28</b>	<b>7.88</b>	<b>28</b>	<b>0.44</b>	<b>28</b>	<b>207.4</b>	<b>207.7</b>	<b>0.03</b>	<b>207.7</b>	<b>191.00</b>	<b>0.0</b>	<b>28</b>	<b>84.04</b>	<b>28</b>	<b>1.44</b>	<b>28</b>
completer	8.13	28	7.51	28	-0.61	28				84.68	28	86.52	28	1.84	28		
non-completer	9.08	8	9.26	8	0.18	8				84.50	8	84.58	8	0.08	8		
no LOCF	7.60	2								102.00	2						
<b>LOCF</b>	<b>8.88</b>	<b>128</b>	<b>7.84</b>	<b>128</b>	<b>0.49</b>	<b>128</b>	<b>208.8</b>	<b>207.7</b>	<b>0.03</b>	<b>207.7</b>	<b>191.00</b>	<b>0.0</b>	<b>128</b>	<b>86.75</b>	<b>128</b>	<b>0.73</b>	<b>128</b>
completer	7.98	113	7.37	115	-0.63	113				86.76	117	87.50	117	0.73	117		
non-completer	8.31	16	8.80	16	0.49	16				86.68	13	87.43	13	0.75	13		
no LOCF	8.53	3								90.80	4						
DJN vs Placebo p=	N.S.		<0.001		<0.001		N.S.		<0.001		<0.001		N.S.		0.18	<0.001	
<b>DJN-180 mg</b>																	
<b>LOCF</b>	<b>8.43</b>	<b>28</b>	<b>7.89</b>	<b>28</b>	<b>0.69</b>	<b>28</b>	<b>204.8</b>	<b>204.3</b>	<b>0.2</b>	<b>204.3</b>	<b>174.0</b>	<b>0.0</b>	<b>28</b>	<b>83.98</b>	<b>28</b>	<b>0.89</b>	<b>28</b>
completer	8.37	33	7.83	35	-0.53	35				83.08	34	83.91	34	0.84	34		
non-completer	9.30	2	9.30	2	0.00	2				31.02	2	82.75	2	1.73	2		
no LOCF	9.30	2								67.90	1						
<b>LOCF</b>	<b>8.08</b>	<b>112</b>	<b>7.40</b>	<b>112</b>	<b>0.67</b>	<b>112</b>	<b>204.3</b>	<b>204.1</b>	<b>0.0</b>	<b>204.1</b>	<b>167.78</b>	<b>0.1</b>	<b>112</b>	<b>83.82</b>	<b>112</b>	<b>0.78</b>	<b>112</b>
completer	8.06	112	7.33	112	-0.73	112				83.47	114	84.10	114	0.62	114		
non-completer	8.21	19	7.83	19	-0.83	19				80.20	18	81.38	18	1.18	18		
no LOCF	7.94	7								88.65	8						
DJN vs Placebo p=	N.S.		<0.001		<0.001		N.S.		<0.001		<0.001		N.S.		<0.001		

LOCF=last observation carried forward  
 no=no prior anti-diabetic medications  
 completer=completed 24 week trial

Table 5  
Efficacy Compared to Associated Safety Parameters: Study 355

	<u>Fructosamine (umol/dl)</u>			<u>Fasting Plasma Glucose (mg/dl)</u>			<u>Weight (kg)</u>			<u>Hypoglycemia</u>									
	<u>Baseline</u>	<u>n</u>	<u>Exit</u>	<u>n</u>	<u>Delta</u>	<u>n</u>	<u>Baseline</u>	<u>n</u>	<u>Exit</u>	<u>n</u>	<u>Delta</u>	<u>n</u>	<u># Events in Study</u>						
<b>Placebo</b>																			
Not-Naive	251.8	17	258.4	19	4.1	17	224.2	19	222.0	19	-2.2	19	85.91	19	85.1	19	-0.82	19	0
Naive	237.4	31	239.1	32	1.9	31	194.4	31	201.5	32	7.7	31	90.53	31	90.40	31	-0.13	31	0
<b>DJN 608</b>																			
Not-Naive	239.2	13	226.2	13	-13.1	13	220.2	13	203.6	13	-16.6	13	97.08	13	97.9	13	0.77	13	0
Naive	225.1	37	210.5	38	-14.9	37	179.2	35	165.1	37	-14.1	35	90.47	37	91.3	37	0.78	37	0
DJN vs Placebo (All) p=	0.082		<0.001		0.002		0.16		0.001		0.03		N.S.		0.14		0.007		
DJN vs Gly (All) p=	0.005		N.S.		<0.001		0.03		0.03		<0.001		0.006		0.007		-0.10		
<b>Glyburide</b>																			
Not-Naive	255.3	19	221.6	19	-33.7	19	234.2	20	166.0	20	-68.3	20	78.09	18	79	19	1.34	18	0
Naive	247.7	30	211.0	30	-36.7	30	203.6	30	147.1	30	-56.5	30	87.06	30	88.8	30	1.69	30	1
Gly vs Placebo (All) p=	N.S.		<0.001		<0.001		N.S.		<0.001		<0.001		0.08		N.S.		<0.001		

Gly=glyburide

**BEST POSSIBLE COPY**

Table 6  
Efficacy Compared to Associated Safety Parameters: Study 351

Placebo	HbA1c (%)					Weight (kg)					Hypoglycemia # Events During Study		
	t=0	n	Exit	n	Delta	n	t=0	n	Exit	n		Delta	n
<b>not-naïve-LOCF</b>	8.43	67	8.28	66	0.44	67	83.99	67	83.99	67	-0.67	67	0
completer	8.17	38	8.89	38	0.70	38	84.71	38	84.70	38	-0.51	38	
non-completer	8.82	29	8.93	29	0.11	29	80.45	29	79.53	29	-0.92	29	
no LOCF	0	0					84.90	4					
<b>naïve-LOCF</b>	8.23	73	8.05	73	0.38	73	86.30	73	86.30	73	-0.28	73	0
completer	8.07	73	8.31	74	0.23	73	86.30	75	86.02	75	-0.28	75	
non-completer	8.58	30	9.04	30	0.46	30	86.58	21	87.49	21	-0.32	21	
no LOCF	0	0					84.64	8					
<b>DJN 120 mg</b>													
<b>not-naïve-LOCF</b>	8.53	57	8.26	57	-0.19	57	83.95	57	84.98	57	1.03	57	0
completer	8.53	57	8.26	57	-0.26	57	83.95	59	84.98	59	1.03	59	
non-completer	9.07	18	9.45	18	0.38	18	81.83	11	80.91	11	-0.85	11	
no LOCF	0	0					82.30	4					
<b>naïve-LOCF</b>	8.15	78	7.31	80	-0.83	78	85.87	82	86.91	82	1.04	82	0
completer	8.15	78	7.31	80	-0.83	78	85.87	82	86.91	82	1.04	82	
non-completer	7.93	24	7.85	24	0.08	24	86.49	17	87.05	17	0.56	17	
no LOCF	0	0					91.40	4					
DJN vs Placebo (all) p=	N.S.		<0.001		<0.001		N.S.		N.S.		<0.001		
DJN vs Metformin (all) p=	N.S.		0.07		<0.001		N.S.		N.S.		<0.001		
DJN vs Combo (all) p=	N.S.		<0.001		<0.001		0.13		N.S.		0.04		
<b>Metformin</b>													
<b>not-naïve-LOCF</b>	8.61	74	7.99	74	-0.99	74	83.99	74	83.99	74	-0.29	74	0
completer	8.73	54	7.68	54	-1.05	54	84.51	56	85.04	56	-0.37	56	
non-completer	9.04	20	8.55	20	-0.50	20	78.51	15	78.50	15	-0.01	15	
no LOCF	0	0						3					
<b>naïve-LOCF</b>	8.21	83	7.30	84	-0.86	83	88.23	84	88.20	84	-0.03	84	4
completer	8.17	83	7.30	84	-0.86	83	88.23	84	88.20	84	-0.03	84	
non-completer	8.49	20	8.17	20	-0.32	20	82.78	14	82.54	14		14	
no LOCF	0	0						6					
Metformin vs Placebo (all) p=	0.19		<0.001		<0.001		N.S.		N.S.		N.S.		
<b>Metformin+DJN 120 mg</b>													
<b>not-naïve-LOCF</b>	8.80	68	7.99	68	-1.59	68	84.38	70	84.26	70	-0.15	70	0
completer	8.91	68	7.19	68	-1.72	68	84.39	68	84.26	68	-0.13	68	
non-completer	8.26	14	7.82	14	-0.44	14	84.38	10	84.10	10	-0.28	10	
no LOCF	0	0						5					
<b>naïve-LOCF</b>	8.19	68	6.78	68	-1.49	68	90.32	68	90.94	68	0.59	68	1
completer	8.21	68	6.59	68	-1.62	68	91.05	68	91.78	68	0.73	68	
non-completer	8.04	21	7.34	21	-0.70	21	86.81	14	86.70	14	-0.11	14	
no LOCF	0	0						7					
Combo vs Placebo (all) p=	0.16		<0.001		<0.001		0.16		0.08		0.04		

\*1 patient each

**BEST POSSIBLE COPY**

Fig. 1

### HgbA1c Values by Treatment Dose and Prior Exposure to Anti-diabetic Drugs: Study 302

