

EQUIDYNE SYSTEMS INC.
TECHNICAL REPORT #006

Rev. #8/7/99

INJEX™ Injector Efficacy Study Technical Report

TABLE OF CONTENTS

SECTION

1. PURPOSE

2. SCOPE

3. ACRONYMS AND DEFINITIONS

4. PERFORMED BY

5. REFERENCES

6. MATERIALS AND METHODS

7. RESULT

8. DISCUSSION OF RESULTS

9. APPENDIX

1. PURPOSE

- 1.1. The purpose of this technical report is to document the results of a clinical study comparing the pharmacokinetics of a fast acting insulin when injected using either a **INJEX™** Injector or a B & D Microfine Syringe.

2. SCOPE

- 2.1. This report applies to the data generated as part of the **INJEX™** Injector Efficacy Clinical Study.

3. ACRONYMS AND DEFINITIONS

- 3.1 None

4. PERFORMED BY:

- 4.1. Equidyne Systems Inc. of San Diego, California, manufacturer of the **INJEX™** Injector System was the Sponsor of the Clinical Study. The company approved all clinical sites, protocols and provided all equipment and supplies for the clinical study.
- 4.2. JB & Associates acted as the Clinical Research Organization for the clinical study. Consultants for JB & Associates authored the study protocol, selected the clinical sites and trained clinical personnel. JB & Associates monitored the clinical sites, collected, analyzed and summarized all clinical data and wrote this technical report.
- 4.3. Clinical Sites and Investigators
 - 4.3.1. Radiant Research
Phoenix, AZ Investigator – Marshall Block, M.D.
 - 4.3.2 Diabetes and Endocrine Associates
San Diego, CA Investigator – Daniel Einhorn, M.D.

5. REFERENCES

- 5.1. **INJEX™** Injector Efficacy Study Protocol, Rev. 1.
- 5.2. **INJEX™** Injector Pain Assessment Technical Report, Rv. 0

6. MATERIAL AND METHODS

Clinical Site

Set-up Prior to the start of testing at a clinical site, all personnel participating in the study were trained by consultants for JB & Associates per the following schedule:

1. Review study objectives
2. Present study protocol
3. Review documentation requirements
4. Review Directions for Use for **INJEX™** System
5. Demonstrate **INJEX™** Injector
6. Practice session with **INJEX™** Injector

After the training session and prior to using the **INJEX™** Injector, each health professional was asked to read the **INJEX™** System User Instruction Manual. After injecting their first subject using the **INJEX™** Injector, the health care professional was asked to complete a Labeling and Ergonomic Assessment Questionnaires. Refer to the Equidyne Systems Pain Assessment Technical Report for the results of the Labeling and Ergonomic Assessment Questionnaires.

SUBJECT INCLUSION/EXCLUSION CRITERIA

A total of 25 Type I and Type II diabetics requiring a fast acting insulin for the management of their diabetes were enrolled in the clinical study that met the following inclusion/exclusion criteria:

Inclusion criteria

1. Type I subjects will be on long term intensive management who have good control.
2. HbA_{1c}'s for Type I diabetic – 3.0 to 9.0
3. Age Range – Over 18 years of age
4. Sex – No restrictions
5. Ethnic Background – No restrictions (Must be able to read and speak English)

Criteria for Exclusion

1. History of hypoglycemia
2. Unable to speak or write English
3. Mental illness that would interfere with following this protocol
4. Children
5. Pregnant women
6. Subjects with an advanced state of diabetes
7. Any subject who has a pre-injection blood glucose reading less than 50 mg/dL or greater than 180 mg/dL

SUBJECT QUALIFICATION

A total of 25 subjects between the age of 21 and 64 were selected with most being Type II diabetics. The subject's were informed of the study objectives and "Experimental Subject's Bill of Rights" by the Clinical Coordinator asked to sign a "Consent to Act as a Research Subject" form. In addition, the INJEX™ Injector was demonstrated to each subject by injecting water into a sponge or stack of tissue.

Subjects were requested to fast prior to testing. Of the 25 subjects, six had either food or glucose tablets prior to testing. There was an even distribution of subjects having food prior to being injected with the **INJEX™** Injector and the syringe.

Prior to the subject's insulin injection, the subject was asked to conduct a blood glucose test on a calibrated blood glucose meter. The protocol stated that if the blood glucose reading was less than 50 mg/dL or greater than 180 mg/dL, the subject was asked to return on another day. One clinical site tested 6 subjects with blood glucose values between 180 and 190 mg/dL. A review of the data for these subjects showed no abnormalities. Therefore, the test results for these subjects were included in the study.

Once qualified, the clinical coordinator drew a blood specimen from the subject and labeled it with the date, subject's initials, and noted as the pre-injection sample.

INJECTION ROUTINE

The subject was able to choose any of the usual sites for the insulin injection (tricep fat pad, upper thigh or buttocks). The injection site was the same for each of the insulin injections. Two of the 25 subjects received their insulin injection in the abdomen. All others were injected in tricep fat pad. The protocol stated that alternating subjects would be injected with the syringe on the first day. One clinical site started a majority of subjects with the syringe versus alternating between the syringe and the **INJEX™**. The reason for the deviation was to entice subjects to return for the second session.

Within ten minutes of passing the blood glucose test, the subject was given their insulin injection by a health care professional. Injections ranged from 3 units to 30 units of Lispro insulin with a majority being in the 4 to 8 unit range. The blood glucose value, injection site, dose, method of injection and time of injection were recorded on the Test Report Form.

ADDITIONAL TESTING

A standardized mixed meal was provided to each subject prior to the twenty (20) minute post injection blood test. The clinical coordinator drew additional blood samples from each subject every 20 minutes for 60 minutes after the insulin injection. All samples were labeled with the date, patient initials and with the number of minutes post insulin injection. In addition, the time of each blood sample was recorded on the Test Report Form. Subjects were requested to return within five days of the first test at approximately the same time and maintain a similar diet for the second test.

POST-TESTING INSTRUCTIONS

On a second day at approximately the same time of day, the subject returned to the clinical site for a second day of testing. The subject's diet for the second test day was recorded on their Patient History Form. The second day of testing was the same as the first with the subject being qualified with a blood glucose test. Once qualified, the subject received their insulin injection from either the **INJEX™** Injector or a syringe. Once again blood samples were taken just prior to the insulin injection and 20, 40 and 60 minutes post injection.

DATA ANALYSIS

Data analysis included calculation of the mean and standard deviation for each group of free insulin level values. This included the pre-injection, 20, 40 and 60 minute post injection reading for both the **INJEX™** Injector and the syringe. The primary null hypothesis was that there is no difference in pharmacokinetics of insulin when injected by either the **INJEX™** Injector or a B & D Microfine Tip Syringe. The alternate hypothesis is that there is a difference in pharmacokinetics of insulin when injected using a **INJEX™** Injector or a B & D Microfine Tip Syringe.

The hypothesis will be tested for statistical significance at the 0.05 Type I level. Efficacy comparisons were based on two-sided tests.

7. RESULTS

A total of 26 subjects received their insulin injection by syringe and the **INJEX™** Injector. One subject did not have a blood sample taken at twenty minutes and was excluded from the efficacy study however was included in the Pain Assessment portion of the study.

The protocol required subjects to fast prior to testing. Six of the subjects did not fast or took glucose tablets prior to testing. Three of the subjects did not fast prior to an injection by syringe and three by the **INJEX™** Injector. Test results for these subjects appeared normal. As part of the qualification process, subjects were to have a blood glucose reading less than 180 mg/dL. A total of five subjects were tested with blood glucose values higher than 180 mg/dL however all blood glucose values were less than or equal to 190 mg/dL. A review of the test results for these subjects did not show any unusual trends. For this reason these subjects were included in both the Efficacy and Pain Assessment Study.

The average age of the subjects was 43 years old with a range of 21 to 64 years old. Twenty-four or 92% of the subjects received their injection in the Tricep fat pad while two subjects or 8% received their injection in the abdomen.

Since only 2 subjects received their injections in the abdomen there was no comparison of data between injection sites.

Each subject received their prescribed insulin dose by both **INJEX™** Injector and syringe on different days. All but two of the subjects received the same dose on both days. The dose distribution was as follows:

Dose	% of Subjects	Dose	% of Subjects
3 units	8	9 units	0
4 units	20	10 units	4
5 units	28	15 units	4
6 units	4	25 units	4
7 units	16	30 units	4
8 units	8		

EFFICACY STUDY

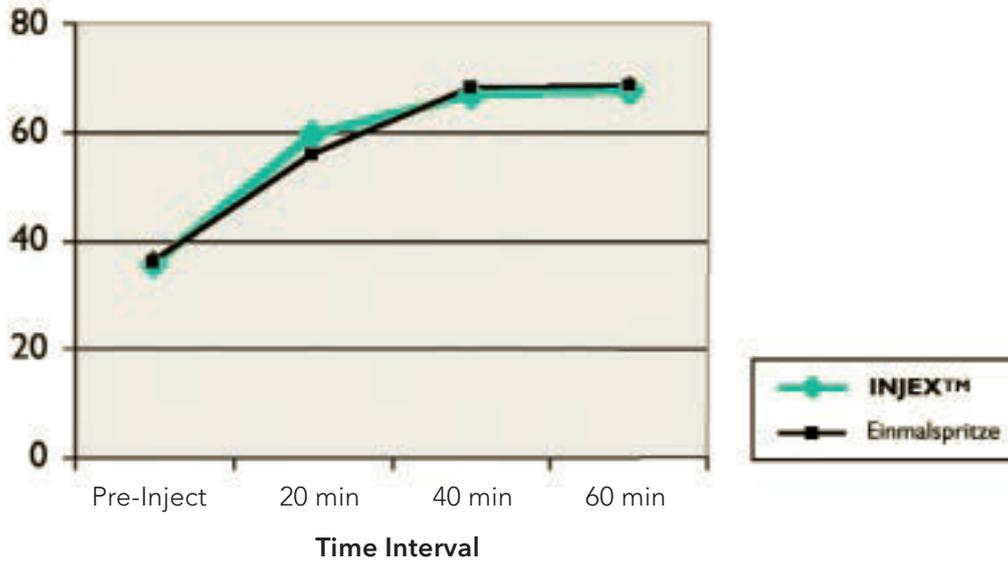
The test results for the efficacy study included the subject's free insulin level just prior to their insulin injection and at 20, 40 and 60 minutes after their insulin injection for both the **INJEX™** Injector and the syringe. The following table shows the pre-injection, 20, 40 and 60 minute post injection average free insulin level and the range of free insulin levels for the **INJEX™** Injector and syringe:

	Average Free Insulin Level (mg/dl)		Free Insulin Level Range (mg/dl)	
	INJEX™ Injector	Syringe	INJEX™ Injector	Syringe
Pre-Injection.0	35.6	36.05	9.8 to 97	9.9 to 92.4
20 minute	59.41	55.55	13.5 to 212.9	15.8 to 148.9
40 minute	66.8	68.2	13.0 to 196.1	9.6 to 231.5
60 minute	67.59	68.39	7.2 to 214.0	8.5 to 252.8

Of the 25 subjects, 14 or 56% had free insulin levels rise at a greater percentage with the **INJEX™** Injector than with the syringe 20 minutes after their insulin injection. In addition, the range of free insulin level values for the **INJEX™** Injector was higher than the syringe. At 40 minutes, 16 or 64% of the subjects receiving their insulin injection by syringe had free insulin levels rise at a greater percentage than with the **INJEX™** Injector. After 60 minutes, 13 or 52% of the subjects receiving their insulin injection by syringe had free insulin level rise at greater percentage than with the **INJEX™** Injector. The range of free insulin level values for the syringe was higher than the **INJEX™** Injector at the 40 and 60 minute time intervals.

Following as a graphical presentation of the average free insulin levels for both the **INJEX™** Injector and the syringe prior to the insulin injection and 20, 40 and 60 minutes after their insulin injection.

Average Free Insulin Level



The following table shows the combination where the percentage of increase for each device was greatest at 20, 40 and 60 minutes post injection:

Combination	# of Subjects	% of Total
INJEX™, INJEX™, Syringe	5	20%
Syringe, Syringe, INJEX™	5	20%
INJEX™, Syringe, Syringe	4	16%
INJEX™, Syringe, INJEX™	4	16%
Syringe, Syringe, Syringe	3	12%
Syringe, INJEX™, INJEX™	2	8%
Syringe, INJEX™, Syringe	1	4%
INJEX™, INJEX™, INJEX™	1	4%

A statistical analysis of the data was conducted to determine if there was a difference in the pharmacokinetics of the insulin level observed after an injection using the **INJEX™** Injector compared to the B & D Microfine Tip Syringe.

The analysis was conducted with a 95 % confidence level. A t-test assuming equal and unequal variances was conducted on the two samples. The hypothesis tested was that $u_1 - u_2 = 0$ where u_1 is the mean level of free insulin observed from subjects receiving an insulin injection from the **INJEX™** Injector and u_2 is the mean level for free insulin observed from subjects receiving an injection from the B & D Microfine Tip Syringe. The size of both samples was 25 subjects.

The result from the t-test, assuming equal and unequal variances for the **INJEX™** Injector and syringe showed the following mean values:

t-test: Two Sample	t-stat value		t critical one tail value		t critical two tail value	
	Equal variances	Unequal variances	Equal variances	Unequal variances	Equal variances	Unequal variances
Pre-Injection	-0.0088	-0.0088	1.6772	1.6772	2.0106	2.0106
20 minute	-0.4357	-0.4357	1.6772	1.6802	2.0106	2.0153
40 minute	0.0819	0.0819	1.6772	1.6772	2.0106	2.0106
60 minute	0.0679	0.0679	1.6772	1.6672	2.0106	2.0106

8. DISCUSSION OF RESULTS

In the efficacy study, two methods of insulin injections were compared with regard to the pharmacokinetics of a fast acting insulin. A total of 25 subjects were given insulin injections on different days using the **INJEX™** Injector and a syringe. Blood tests were performed on each subject prior to the insulin injection and at 20, 40 and 60 minutes after the insulin injection.

The results of the study showed that the average free insulin level prior to the injection and at 20, 40 and 60 minutes after an insulin injection using the **INJEX™** Injector and a syringe were equivalent. The average free insulin level prior to an injection for the **INJEX™** Injector was 35.6 mg/dL compared to 36.1 for the syringe. At twenty minutes after the insulin injection, the average free insulin level for the **INJEX™** Injector was 59.4 compared to 55.5 for the syringe. At twenty minutes, an injection by the **INJEX™** Injector provided a 7% higher average free insulin level. In addition, the range of free insulin level values for the **INJEX™** Injector was higher than the syringe at the 20 minute time interval.

At forty and sixty minutes, the syringe provided a 2% and 1% higher average free insulin level respectively. The syringe also had a higher range of free insulin level values than the **INJEX™** Injector at the 40 and 60 minute time interval. The average free insulin level for the **INJEX™** Injector and the syringe show that the pharmacokinetics for the **INJEX™** Injector is slightly faster than the syringe in the first twenty minutes after an injection of Lispro fast acting insulin. The data also shows that the pharmacokinetics of insulin from an injection by syringe equals that of the **INJEX™** Injector within forty minutes.

The average free insulin level data suggests that there may be a higher absorption rate of the insulin after an injection from an **INJEX™** Injector in the first twenty minutes than a syringe. However, when you look at the combination of percentage increases over the entire 60 minute period, there was no combination that dominated. In fact, every possible combination was achieved. There were the same number of subjects with the **INJEX™** Injector, **INJEX™** Injector and syringe combination as the syringe, syringe an **INJEX™** Injector combination.

This data suggests that there is little or no difference in the pharmacokinetics of a fast acting insulin when injected with either the **INJEX™** Injector or the syringe.

TECHNICAL REPORT **INJEX PHARMA**

INJEX PHARMA GMBH

Buckower Damm 114

12349 Berlin – Deutschland

info@injex.de

www.spritze-ohne-nadel.de