Summary ID# 9673

Clinical Study Summary: Study H9D-MC-ITAB

Complaints Associated with Use of the Prefilled Pen B When Used by Patients with Type 2 Diabetes on Twice-Daily Insulin Therapy

Date summary approved by Lilly: 27 September 2006

Brief Summary of Results

This was a Phase 3, open-label, one-period (7 to 9 weeks), three-visit, non-comparative (all patients used the same study pen type) study in which patients with type 2 diabetes used the Prefilled Pen B to inject insulin lispro low mixture (LM) (75% insulin lispro protamine suspension [NPL] and 25% insulin lispro injection [rDNA origin]) in take-home situations. The primary objective of the study was to collect complaint data on the Prefilled Pen B when used by persons with type 2 diabetes to self-administer insulin for 2 months.

- Based on patients' experience with the pens during the study, 114 complaints associated with 96(2.1%) Prefilled Pen Bs were reported by 58 patients (17%).
- A total of 342 patients used 4569 Prefilled Pen Bs at least once in the study. Patients used the Prefilled Pen B for a mean 8.0 ± 1.6 weeks, and 2642.6 total patient-weeks.
- One hundred sixteen episodes of hypoglycemia were reported during the study, at a rate of 0.67 episodes per patient per 30 days for all patients combined. Seven severe hypoglycemia events were reported by 4 patients.

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- Twenty-five Prefilled Pen B-related hypoglycemic events were reported by 4 patients. Relatedness to the Prefilled Pen B was determined in the opinion of the investigator.
- Three patients reported 13 Prefilled Pen B-related hyperglycemic events.
- There were no deaths. Two patients experienced three serious adverse events (SAEs) during the trial. Both patients were hospitalized (1 for chest discomfort, 1 for gastroenteritis and syncope). None of the events were considered related to protocol, insulin therapy, or the study device, and neither of these patients discontinued.
- One patient discontinued due to an adverse event, hyperglycemia, that was considered related to the study device.
- The most frequently reported Treatment-Emergent Adverse Events (TEAEs) (>2%) were hypoglycemia and nasopharyngitis.
- Patients rated the extent of their satisfaction with using the Prefilled Pen B by rating to what extent they agreed with individual features. The three most highly rated responses were easy to see the amount or dose of insulin taken (88.8% agreed), convenient for me to use (88.1% agreed), and easy to fit into daily life (87.8% agreed). Eighty-five percent of patients responded that they were confident that they received the correct dose with Prefilled Pen B. Patients rated device interaction by selecting the top 3 reasons to use Prefilled Pen B: easy to use (24.3%), easy to read numbers (17.0%), and easy to push the dose knob/inject (15.4%). The user manual was rated easy to use by 75.5% of patients who responded. Patients rated the user manual by selecting the top 3 suggestions for improvement to the user manual: no improvement needed (29.0%), larger print (19.0%), and more compact (13.4%).

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Title of Study: Complaints Associated with Use of the Prefilled Pen B When Used by Patients with Type 2 Diabetes on Twice-Daily Insulin Therapy	
Investigator(s): This multicenter study included 40 principal investigators.	
Study Center(s): This study was conducted at 40 study centers in 5 countries.	
Length of Study: 32 weeks 1 day Date of first: 13 September 2005 Date of last: 26 April 2006	**Phase of Development:** 3
Objectives: The primary objective was to collect complaint data on the Prefilled Pen B when used by persons with type 2 diabetes to self-administer insulin in take-home situations for 2 months. These data contributed to the evaluation of the Prefilled Pen B prior to launch. The secondary objectives of the study were • to monitor safety, including all adverse events, hypoglycemia, device-related hypoglycemia, and device-related hyperglycemia, • to assess overall patient perception of the device's performance through a patient questionnaire.	
Study Design: This was a Phase 3, open-label, one-period (7 to 9 weeks), three-visit, noncomparative (all patients used the same study pen type) study in which approximately 370 patients with type 2 diabetes used the Prefilled Pen B to inject insulin lispro LM in take-home situations.	
Number of Patients: Planned: 370 patients using Prefilled Pen B with no direct treatment comparisons, (320 patients were expected to complete the protocol). Enrolled: 346 patients received a Prefilled Pen B, 4 patients discontinued before using the Prefilled Pen B once, 342 patients used Prefilled Pen B to inject insulin lispro LM, of those, 250 patients had prior insulin pen experience (PIPE), and 92 patients had no prior insulin pen experience (NPIPE). Completed: 309 patients (PIPE: 225, NPIPE: 84).	
Diagnosis and Main Criteria for Inclusion: Patients with type 2 diabetes mellitus as defined by the World Health Organization (Bennett 1991) were eligible to participate in this study if they were 25 to 75 years old, inclusive; were already on any formulation of Lilly insulin (one or two injections a day of one or two types of insulin) or were beginning insulin therapy; had an HbA_{1c} value up to 1.75 times the upper limit of normal (ULN) reference range at the local laboratory within 30 days prior to Visit 1 for patients already on insulin therapy; had an HbA_{1c} value from 1.25 to 1.75 times the ULN reference range at the local laboratory within 30 days prior to Visit 1 for patients new to insulin therapy; were able and willing to self-inject with the Prefilled Pen B device and use the patient diary; were considered by the investigator to be well-motivated to attain and maintain good blood glucose control using regular blood glucose monitoring and, adjust insulin dose as needed; and had provided written informed consent to participate in this study.	
Test Device, Dose, and Mode of Administration: Prefilled Pen B was used to subcutaneously inject insulin lispro LM within 15 minutes prior to the morning and evening meals. The initial dose was established by the investigator. Subsequently, investigators were allowed to adjust the insulin dose based on the needs of the individual patient.	
Reference Device: This was a noncomparative study. All patients used the same study pen type.	
Duration of Treatment: 7 - 9 weeks	

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Variables:

The primary measure was to collect complaints related to use of the Prefilled Pen B among persons with type 2 diabetes who used the pen to self-administer insulin in take-home situations for 2 months. A device complaint was defined as any written, electronic, or oral communication that alleged deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device.

A complaint category was assigned by the sponsor's Quality group based on the information provided in the complaint report, and an analysis category was also assigned to each complaint based on a the sponsor's engineering assessment of the reported complaint and assessment of the Prefilled Pen B, if it was returned. When no pen was available, analysis categories were assigned based on an engineering evaluation of the information provided in the complaint and information on file from similar complaints. All reported complaints were collected and classified as functional, nonfunctional, or Direction For Use (DFU)-related based on information contained in the complaint report and the engineering evaluation.

- Functional complaints were defined as complaints related to a device malfunction, whether real or alleged, or failure of the device to meet performance specifications (for example, pen jam).
- Non-functional complaints were defined as complaints related to either a cosmetic concern or perception concern, whether real, implied, or alleged (for example, pen color).
- DFU complaints were defined as complaints related to the DFU legibility, clarity, or any other usability defect (for example, font is too small).

Secondary measures were safety and overall patient perception of the device's performance. Safety measures included adverse event reports, hypoglycemia events, device-related hypoglycemia events, and device-related hyperglycemia episodes. A patient questionnaire was used to assess overall patient perception of the device's performance based on satisfaction, confidence, user interaction (Prefilled Pen B features), and DFU.

Evaluation Methods:

Statistical: Because this was a one-arm study with no direct treatment comparisons, a formal power calculation was not performed. However, with a sample size of 320 patients (completers), if no serious functionality complaints were reported in this study, then there was a 96% confidence level that a serious functionality complaint would not occur in more than 1% of the Prefilled Pen B user population. A serious functionality complaint was defined as a complaint in which the pen was not able to deliver the desired dose, the patient did not detect the problem until after use, and there was a significant safety concern. This calculation was derived based on a binomial distribution, which was appropriate given the potentially large (true) Prefilled Pen B user population. Approximately 370 randomized patients were planned to allow for dropouts during the study. All analyses were conducted on the full analysis set including all data from all enrolled patients injecting at least one dose of insulin with the Prefilled Pen B. Complaints assessed to be related to functionality were summarized using descriptive statistics for the frequency (sample size, mean, standard deviation, maximum, minimum, and median) and incidence (sample size, proportion, and 95% confidence interval). Analyses similar to those described above were also performed for Prefilled Pen B complaint types that were not related to functionality (nonfunctionality) and those that were related to the DFU. Patient perception of the device's performance measurements were assessed by reporting descriptive statistics for individual items in all four sections of the patient questionnaire: Satisfaction, Confidence, User Interaction (Prefilled Pen B features), and DFU. Subgroup analyses were performed by prior insulin experience, prior insulin pen experience, and by country. Subgroup analyses were similar to the analyses described above. All tests of subgroup effects were conducted at a two-sided alpha level of 0.05 unless otherwise stated. A Fisher's exact test was utilized if computationally feasible. (Otherwise, the Pearson's chi-square test was utilized.)

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Results:

Patient Demographics

Patient demographic data are provided in Table 1.

Table 1. Baseline Patient Demographics, All Patients Who Used the Prefilled Pen B at Least Once (N = 342)

Variable	
Mean age ± SD (range), years	59.6 ± 10.7 (26.6 – 77.5)
Number Male, N (%)	174 (50.9)
Number Female, N (%)	168 (49.1)
Weight ± SD (range), kg	89.1 ± 22.3 (50.0 – 185.0)
BMI kg/m^2 ± SD (range)	32.0 ± 7.0 (18.8 - 59.8)
BMI group N (%):	
≤30 kg/m^2	142 (41.8)
>30 kg/m^2	198 (58.2)
Ethnic origin N (%):	
Caucasian	244 (71.4)
Hispanic	54 (15.8)
African descent	25 (7.3)
East/Southeast Asian	8 (2.3)
Other	7 (2.1)
Western Asian	4 (1.2)
Prior Insulin Experience	297 (86.8)
Prior Insulin Pen Experience	250 (73.1)
Mean duration of diabetes ± SD (range), years	13.3 ± 8.5 (0.1 – 50.0)
Mean duration of use of prestudy insulin delivery device ± SD (range), years	3.0 ± 3.9 (0.0 – 26.0)

Abbreviations: BMI = body mass index; N = number; SD = standard deviation.

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Patient Disposition

The disposition of all entered patients is diagramed in Figure 1, and reasons for discontinuation of all patients who received a Prefilled Pen B are given in Table 2.

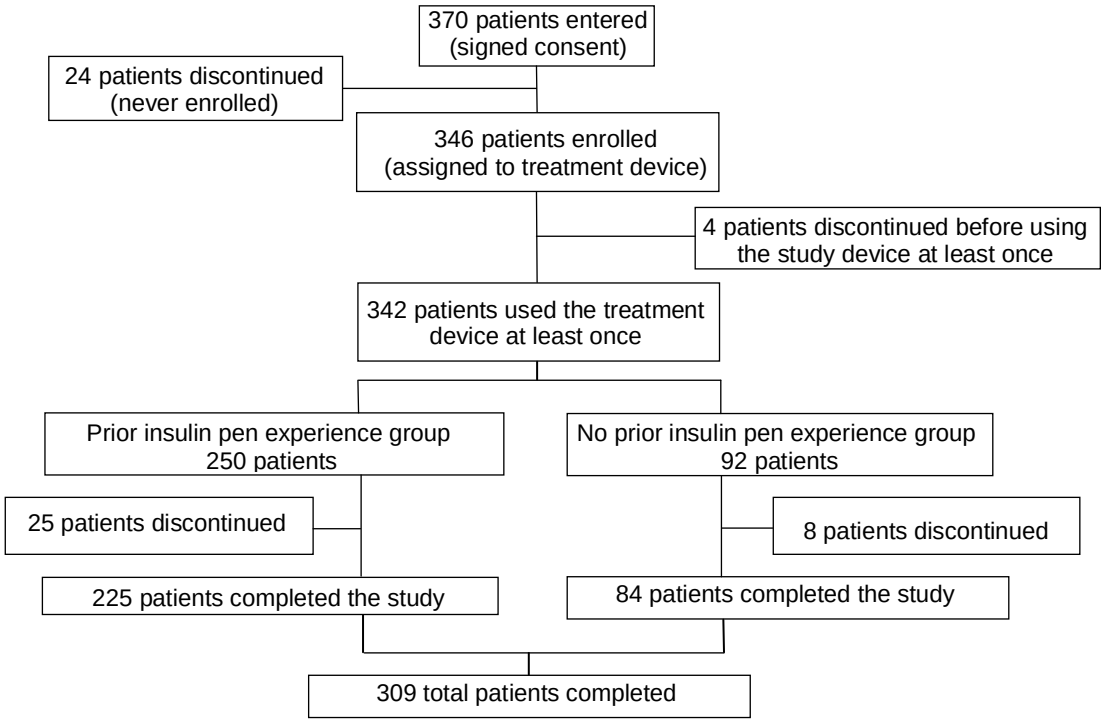

Figure 1. Patient disposition.

Table 2. Summary of Reasons for Study Discontinuation, All Enrolled Patients

Primary Reason for Discontinuation	Number of Patients
Protocol completed	309
Protocol entry criteria not met	11
Protocol violation	3
Personal conflict or other patient decision	13
Physician decision	4
Adverse event	1
Unable to contact patient (lost to follow up)	1
Discontinued before using the PPB at least once per study protocol	
Personal conflict or other patient decision	1
Unable to contact patient (lost to follow up)	3

Abbreviation: PPB = Prefilled Pen B.

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Primary Measures

A total of 342 patients used 4569 Prefilled Pen Bs at least once in the study. Based on patients' experience with the pens during the study, 114 complaints associated with 96 (2.1%) Prefilled Pen Bs were reported by 58 patients (17%). Complaints reported during the study are summarized in Table 3. Details pertaining to function-related complaints are presented in Table 4, nonfunction related complaints are presented in Table 5, and directions for use-related complaints are presented in Table 6.

Table 3. Primary Endpoints: Summary of Complaints Reported

Category	N (%)
Total complaints reported, Functional, Non-Functional, and DFU combined	114 (100%)
Functional complaints received	76 (66.7)
Non-Functional complaints received	37 (32.5)
Directions for Use complaints received	1 (0.9)
Total PPBs that were used by a patient at least once	4569 (100%)
Total PPBs that were associated with no complaints	4473 (97.9)
Total PPBs that were associated with one or more complaint(s)	96 (2.1)
PPBs associated with a Functional complaint	66 (1.4)
PPBs Associated with a Non-Functional Complaint	33 (0.7)[a]
PPBs Associated with a DFU Complaint	1 (0.2)
Total patients who used the PPB at least once	342 (100%)
Total patients who reported no complaints	284 (83.0)
Total patients who reported one or more complaints	58 (17.0)
Prior insulin pen experience	51 (14.9)
No prior insulin pen experience	7 (2.0)
Patients who reported one or more Functional complaints	48 (14.0)
Prior insulin pen experience	42 (12.3)
No prior insulin pen experience	6 (1.8)
Patients who reported one or more Non-Functional complaints	17 (5.0)[b]
Prior insulin pen experience	16 (4.7)
No prior insulin pen experience	1 (0.3)
Patients who reported one or more DFU complaints	1 (0.3)
Prior insulin pen experience	1 (0.3)
No prior insulin pen experience	0 (0)

Abbreviations: DFU = Directions for Use; N = number of complaints; PPB = Prefilled Pen B.

[a] Four of these pens also had at least one Functional complaint.

[b] Eight of these patients also had at least one Functional complaint.

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Table 4. Primary Endpoints: Function-Related Prefilled Pen B Complaints (N = 76)

Complaint Category	Number of Complaints		Analysis Category
Dose Knob	28	13	Injection button detached.
		2	Difficult to dial; Needle not attached or completely attached; Pen jammed.
		6	No product returned[a].
		1	Normal (No abnormalities noted of the device appearance or function).
		2	Injection button detached; No product returned[a].
		1	No product returned[a]; Patient education issue.
		1	Device meets functional requirements; Device meets glide force specifications; Injection force within expected limits; Normal.
		2	Device meets functional requirements.
Device Not Working	11	8	Difficult to dial; Needle not attached or completely attached; Pen jammed.
		1	Out of specification for injection force (elevated glide force); Spring damaged.
		1	Device meets functional requirements; Device meets glide force specifications; Injection force within expected limits; Normal.
		1	Pen Jammed.
Cap Broken	6	3	Cap tight; Normal.
		1	Cap damaged; No product returned[a].
		2	Cap tight; No product returned[a]; Normal.
Cap Removal	5	2	Cap tight; Normal.
		2	Cap tight; No product returned[a].
		1	Cap damaged; Cap tight; No product returned[a].
Device Broken	5	1	Glue bond failure.
		3	Injection button detached.
		1	Injection button detached; No product returned[a].
Injection Force High	4	3	No product returned[a].
		1	No product returned[a]; Patient education issue.
Clicks	2	2	No product returned[a]; Other (no analysis category is appropriate).
Injection Button	1	1	Injection button detached.
Cartridge Empty	2	2	Cartridge empty due to use.

(continued)

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Table 4. Primary Endpoints: Function-Related Prefilled Pen B Complaints (Concluded)

Complaint Category	Number of Complaints		Analysis Category
Device Delivers Less Than Selected	1	1	Difficult to dial; Needle not attached or completely attached; Pen jammed.
Device Defective	1	1	Normal.
Broken, Defective, Not Working	1	1	Injection button detached.
Injection Screw Not Moving	1	1	Difficult to dial; Needle not attached or completely attached; Pen jammed.
Injection Force High, Priming Difficulty	1	1	Normal.
Ergonomic, Injection Force High	1	1	No product returned[a]; Patient education issue.
Priming Difficulty	1	1	Device meets functional requirements; Device meets glide force specifications; Injection force within expected limits; Normal.
Cap Broken, Device Broken	1	1	Injection button detached.
Cap Broken, Cap Removal	1	1	Cap tight; Normal.
End Cap Attachment	1	1	Injection button detached.
Appearance - Red Discoloration	1	1	Appearance - red discoloration (Blood found in cartridge); difficult to dial.
Other	1	1	No product returned[a].

[a] Prefilled Pen B was not sent to Quality Control for a technical assessment of the reported complaint.

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Table 5. Primary Endpoints: Non-Functionality-Related Prefilled Pen B Complaints (N = 37)

Complaint Category	Number of Complaints		Analysis Category
Unspecified	17	17	Normal.
Scale not readable or understandable	6	5	Aesthetic defect (Any cosmetic damage to any part of the device, that has no effect on performance); No product returned [a].
		1	No product returned.
Clicks, Other	5	5	Normal.
Dose Knob	3	1	Normal (No abnormalities noted of the device appearance or function).
		2	Aesthetic defect; No product returned [a]; Other (no analysis category is appropriate).
Device Size	2	1	Aesthetic defect; No product returned [a].
		1	No product returned [a].
Clicks	1	1	Dose knob detached.
Clicks, Scale not readable or understandable	1	1	Cap tight; No product returned [a].
Air Bubble Removal	1	1	Cartridge bubble (Air bubbles observed in the cartridge); No product returned [a]; Patient education issue.
Device Weight	1	1	No product returned [a].

[a] Prefilled Pen B was not sent to Quality Control for a technical assessment of the reported complaint.

Table 6. Primary Endpoints: Direction for Use-Related Prefilled Pen B Complaints

Complaint Category	Number of Complaints		Analysis Category
Does Not Understand How to Use Device	1	1	No product returned[a].

[a] Prefilled Pen B was not sent to Quality Control for a technical assessment of the reported complaint.

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Secondary Measures

Overall patient perception of the device's performance was evaluated through a questionnaire completed at endpoint. The questionnaire had four sections pertaining to the following:

- **satisfaction** (ranked from 1-7: strongly disagree to strongly agree; and from 1-5: very difficult to very easy),
- **confidence** (ranked from 1-7: not at all confident to very confident),
- **user interaction** (ranked top 3 reasons to use the Prefilled Pen B), and
- **user manual** (ranked from 1-7: not at all easy to very easy; and up to three improvements for user manual).

The above 5- and 7- point scales were also analyzed in 3-point response groups combining all positive responses, all negative responses, and those that were neither positive nor negative.

Patients rated the extent of their satisfaction with using the Prefilled Pen B by rating to what extent they agreed with individual features (easy to see the amount or dose of insulin taken: 88.8% agreed, convenient for me to use: 88.1% agreed, easy to fit into daily life: 87.8% agreed) (Table 7).

At endpoint, 85% of patients responded that they were confident that they received the correct dose with Prefilled Pen B (Table 8).

Patients rated device interaction by selecting the top three reasons to use Prefilled Pen B: easy to use (24.3%), easy to read numbers (17.0%), and easy to push the dose knob/inject (15.4%) (Table 9).

The user manual was rated easy to use by 75.5% of patients who responded. Patients rated the user manual by selecting the top three suggestions for improvement to the user manual: no improvement needed (29.0%), larger print (19.0%), and more compact (13.4%) (Table 10).

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Table 7. Secondary Endpoints: Patient Satisfaction Evaluated at Endpoint

Questions	Disagree N (%)	Neither N (%)	Agree N (%)
Based on your experience with the Prefilled Pen B, to what extent do you agree that the Prefilled Pen B has these features?			
Easy to see amount or dose of insulin to be taken.	8 (2.6)	27 (8.7)	276 (88.8)
Prior insulin pen experience	7 (3.1)	24 (10.6)	195 (86.3)
No prior insulin pen experience	1 (1.2)	3 (3.5)	81 (95.3)
Convenient for me to use.	6 (1.9)	31 (10.0)	274 (88.1)
Prior insulin pen experience	3 (1.3)	26 (11.5)	197 (87.2)
No prior insulin pen experience	3 (3.5)	5 (5.9)	77 (90.6)
Easy to fit into my daily life.	3 (1.0)	35 (11.3)	273 (87.8)
Prior insulin pen experience	2 (0.9)	28 (12.4)	196 (86.7)
No prior insulin pen experience	1 (1.2)	7 (8.2)	77 (90.6)
Does not interfere with plans for short trips, less than 100 miles (161 km), from home	3 (1.0)	41 (13.2)	267 (85.9)
Prior insulin pen experience	3 (1.3)	32 (14.2)	191 (84.5)
No prior insulin pen experience	0 (0.0)	9 (10.6)	76 (89.4)
Easy to carry for use away from home.	7 (2.3)	37 (11.9)	266 (85.8)
Prior insulin pen experience	7 (3.1)	31 (13.7)	188 (83.2)
No prior insulin pen experience	0 (0.0)	6 (7.1)	78 (92.9)
Helps me manage my diabetes at home	8 (2.6)	66 (21.2)	237 (76.2)
Prior insulin pen experience	7 (3.1)	49 (21.7)	170 (75.2)
No prior insulin pen experience	1 (1.2)	17 (20.0)	67 (78.8)
Reduces my reluctance to take injections.	29 (9.4)	66 (21.3)	215 (69.4)
Prior insulin pen experience	16 (7.1)	61 (27.1)	148 (65.8)
No prior insulin pen experience	13 (15.3)	5 (5.9)	67 (78.8)
Not noticeable to others when used.	14 (4.5)	83 (26.8)	213 (68.7)
Prior insulin pen experience	9 (4.0)	68 (30.2)	148 (65.8)
No prior insulin pen experience	5 (5.9)	15 (17.7)	65 (76.5)
Reduces embarrassment and self-consciousness when used away from home.	23 (7.4)	73 (23.6)	213 (68.9)
Prior insulin pen experience	15 (6.7)	61 (27.2)	148 (66.1)
No prior insulin pen experience	8 (9.4)	12 (14.1)	65 (76.5)
Easy to control my blood sugar.	19 (6.1)	104 (33.6)	187 (60.3)
Prior insulin pen experience	15 (6.6)	73 (32.3)	138 (61.1)
No prior insulin pen experience	4 (4.8)	31 (36.9)	49 (58.3)

(continued)

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Table 7. Secondary Endpoints: Patient Satisfaction Evaluated at Endpoint (Concluded)

Questions	Difficult N (%)	Neither N (%)	Easy N (%)
How would you rate the Prefilled Pen B on each of the following?			
Learning to use the pen.	6 (1.9)	10 (3.2)	294 (94.8)
Prior insulin pen experience	2 (0.9)	7 (3.1)	216 (96.0)
No prior insulin pen experience	4 (4.7)	3 (3.5)	78 (91.8)
Overall use.	6 (1.9)	20 (6.5)	284 (91.6)
Prior insulin pen experience	4 (1.8)	15 (6.7)	206 (91.6)
No prior insulin pen experience	2 (2.4)	5 (5.9)	78 (91.8)
Selection of dose.	7 (2.3)	10 (3.2)	292 (94.5)
Prior insulin pen experience	5 (2.2)	8 (3.6)	211 (94.2)
No prior insulin pen experience	2 (2.4)	2 (2.4)	81 (95.3)
Ability to read the dose numbers.	8 (2.6)	14 (4.5)	288 (92.9)
Prior insulin pen experience	7 (3.1)	12 (5.3)	206 (91.6)
No prior insulin pen experience	1 (1.2)	2 (2.4)	82 (96.5)
Use of the user manual/directions that came with the pen.	7 (2.3)	31 (10.1)	270 (87.7)
Prior insulin pen experience	5 (2.2)	23 (10.3)	195 (87.4)
No prior insulin pen experience	2 (2.4)	8 (9.4)	75 (88.2)
Holding the pen while injecting.	19 (6.1)	25 (8.1)	266 (85.8)
Prior insulin pen experience	12 (5.3)	18 (8.0)	195 (86.7)
No prior insulin pen experience	7 (8.2)	7 (8.2)	71 (83.5)
Injecting the dose.	21 (6.8)	13 (4.2)	276 (89.0)
Prior insulin pen experience	15 (6.7)	10 (4.4)	200 (88.9)
No prior insulin pen experience	6 (7.1)	3 (3.5)	76 (89.4)
	Number of patients responding to at least 1 question = 311		

Abbreviation: N = number of patients.

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Table 8. Secondary Endpoints: Patient Confidence Evaluated at Endpoint

Question	Not Confident N (%)	Neither N (%)	Confident N (%)
How confident are you that you receive the correct dose with your Prefilled Pen B?	2 (0.7)	45 (14.5)	263 (84.8)
Prior insulin pen experience	2 (0.9)	36 (16.0)	187 (83.1)
No prior insulin pen experience	0 (0.0)	9 (10.6)	76 (89.4)
			Number of patients responding = 310

Abbreviation: N = number of patients.

Table 9. Secondary Endpoints: User Interaction Evaluated at Endpoint

Questions	Prior insulin pen experience N (%)	No prior insulin pen experience N (%)	Combined N (%)
Select the top 3 reasons you would use the Prefilled Pen B (Select no more than 3).			
Easy to use	145 (24.2)	50 (24.4)	195 (24.3)
Easy to read numbers	109 (18.2)	28 (13.7)	137 (17.0)
Easy to push the dose knob/inject	102 (17.0)	22 (10.7)	124 (15.4)
Can dial back easily without wasting insulin	70 (11.7)	24 (11.7)	94 (11.7)
Easy to learn to use	46 (7.7)	22 (10.7)	68 (8.5)
Easy to carry	30 (5.0)	29 (14.2)	59 (7.3)
Size	25 (4.2)	7 (3.4)	32 (4.0)
Easy to hold	24 (4.0)	8 (3.9)	32 (4.0)
Confidence that I received the correct dose	18 (3.0)	2 (1.0)	20 (2.5)
Weight	14 (2.3)	5 (2.4)	19 (2.4)
Appearance of the pen	9 (1.5)	5 (2.4)	14 (1.7)
Can use 31 gauge needle	5 (0.8)	1 (0.5)	6 (0.7)
Would not use the Prefilled Pen B	2 (0.3)	2 (1.0)	4 (0.5)
Number of Responses	599	205	804

Abbreviation: N = number of patients.

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Table 10. Secondary Endpoints: User Manual Evaluated at Endpoint

Questions	Prior insulin pen experience N (%)	No prior insulin pen experience N (%)	Combined N (%)
How would you rate the ease of the User Manual?			
Easy	165 (74.3)	66 (78.6)	231 (75.5)
Neither	56 (25.2)	17 (20.2)	73 (23.9)
Not at all easy	1 (0.5)	1 (1.2)	2 (0.7)
Number of Responses	222	84	306
Select what should be done to IMPROVE the Prefilled Pen B user manual (Select no more than 3).			
No improvement needed	110 (31.0)	35 (24.1)	145 (29.0)
Larger print	62 (17.5)	33 (22.8)	95 (19.0)
More compact	49 (13.8)	18 (12.4)	67 (13.4)
More pictures	30 (8.5)	12 (8.3)	42 (8.4)
More detail in the descriptions	25 (7.0)	17 (11.7)	42 (8.4)
More color	29 (8.2)	11 (7.6)	40 (8.0)
More questions and answers	24 (6.8)	9 (6.2)	33 (6.6)
Less detail in the descriptions	10 (2.8)	2 (1.4)	12 (2.4)
Easier wording	7 (2.0)	2 (1.4)	9 (1.8)
Less color	4 (1.1)	4 (2.8)	8 (1.6)
Larger pictures	4 (1.1)	1 (0.7)	5 (1.0)
Less pictures	1 (0.3)	1 (0.7)	2 (0.4)
Number of Responses	355	145	500

Abbreviation: N = number of patients.

Safety

One hundred sixteen episodes of hypoglycemia (PIPE: 78; NPIPE: 38) were reported during the study (Table 11), at a mean rate of 0.67 episodes per patient per 30 days for all patients combined (PIPE: 0.53; NPIPE: 1.04) (Table 12 and Table 13). Seven severe hypoglycemia events that were not related to the Prefilled Pen B were reported by 4 patients (Table 14). Severe hypoglycemia was defined as hypoglycemia where the patient required assistance from another person **and** which was associated with either a blood glucose level less than 2.8 mmol/L (50 mg/dL) **or** prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. This definition included all episodes in which neurologic impairment was severe enough to prevent self-treatment and which were therefore thought to put patients at risk of injuring themselves or others ([DCCT] 1991).

Twenty-five Prefilled Pen B-related hypoglycemic events were reported by 4 patients (Table 15). Prefilled Pen B-related hypoglycemia was defined as any time a patient felt, or another person observed, that the patient was experiencing a sign/symptom that he/she associated with hypoglycemia or a blood glucose measurement less than 3.5 mmol/L (63 mg/dL), and the relatedness was judged by the investigator.

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Three patients reported 13 Prefilled Pen B-related hyperglycemic events (Table 16). Hyperglycemia is defined as a blood glucose measurement greater than 18 mmol/L (324 mg/dL), and relatedness is determined by the investigator

There were no deaths. Two patients experienced three SAEs during the trial. Both patients were hospitalized (1 for chest discomfort, 1 for gastroenteritis and syncope). None of the events were considered related to protocol, insulin therapy, or the study device, and neither of these patients discontinued (Table 17).

One patient discontinued due to an adverse event, hyperglycemia, that was not considered related to protocol or insulin therapy, but was considered related to the study device (Table 18).

The most frequently reported TEAEs (≥2%) were hypoglycemia (PIPE: 3.6%, NPIPE: 6.5%, combined: 4.4%) and nasopharyngitis (PIPE: 3.6%, NPIPE: 2.2%, combined: 3.2%) (Table 19).

Patients used the Prefilled Pen B for a mean 8.0 ± 1.6 weeks, and 2642.6 total patient-weeks (Table 20).

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Table 11. Summary and Analysis of Incidence of All Reported Hypoglycemic Episodes by Visit and Overall;

Visit	--- Prior Insulin Pen Experience --- Yes n(%)	No n(%)	Fisher's exact p-value
Visit 2			
Number of Patients	250	92	0.276
Number of Patients with Episodes	65 (26.00)	30 (32.61)	
Number of Patients without Episodes	185 (74.00)	62 (67.39)	
Visit 3			
Number of Patients	230	85	0.277
Number of Patients with Episodes	45 (19.57)	22 (25.88)	
Number of Patients without Episodes	185 (80.43)	63 (74.12)	
Endpoint(LOCF)			
Number of Patients	250	92	0.456
Number of Patients with Episodes	50 (20.00)	22 (23.91)	
Number of Patients without Episodes	200 (80.00)	70 (76.09)	
Overall			
Number of Patients	250	92	0.094
Number of Patients with Episodes	78 (31.20)	38 (41.30)	
Number of Patients without Episodes	172 (68.80)	54 (58.70)	

Abbreviations: LOCF = last postbaseline measurement carried forward; n = total number of patients within the specified group per visit.

Note: Overall refers to the patient's values/responses for the entire study and is not associated with a particular visit.

Hypoglycemia is defined as any time a patient feels; or another person observes;that the patient is experiencing a sign/symptom that he/she would associate with hypoglycemia or a blood glucose measurement less than 3.5 mmol/L (63mg/dL).

Table 12. Summary of Rate of Hypoglycemia Episodes

Hypoglycemia Rate	Visit 2	Visit 3	Endpoint (LOCF)
Number of Patients	342	315	342
Mean	0.92	0.68	0.67
Median	0.00	0.00	0.00
Maximum	17.59	13.64	13.64
Minimum	0.00	0.00	0.00
Standard Deviation	2.23	1.89	1.86
Standard Error Mean	0.12	0.11	0.10

Abbreviation: LOCF = last observation carried forward.

Hypoglycemia is defined as any time a patient feels; or another person observes; that the patient is experiencing a sign/symptom that he/she would associate with hypoglycemia or a blood glucose measurement less than 3.5 mmol/L (63 mg/dL).

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Table 13. Summary and Analysis of Rate of All Reported Hypoglycemic Episodes by Visit; Comparison of Prior Insulin Pen Experience

Prior Insulin Pen Experience	Hypoglycemia Rate	Visit 2	Visit 3	Endpoint (LOCF)
Yes				
	Number of Patients	250	230	250
	Mean	0.84	0.51	0.53
	Median	0.00	0.00	0.00
	Maximum	17.14	8.57	8.57
	Minimum	0.00	0.00	0.00
	Standard Deviation	2.02	1.40	1.43
	Standard Error Mean	0.13	0.09	0.09
No				
	Number of Patients	92	85	92
	Mean	1.15	1.12	1.04
	Median	0.00	0.00	0.00
	Maximum	17.59	13.64	13.64
	Minimum	0.00	0.00	0.00
	Standard Deviation	2.72	2.78	2.68
	Standard Error Mean	0.28	0.30	0.28
	p-value*	0.244	0.011	0.025

Abbreviation: LOCF = last observation carried forward.

*p-values were obtained from non-parametric rank transformation analysis of variance (ANOVA) model with prior insulin pen experience.

Hypoglycemia is defined as any time a patient feels; or another person observes; that the patient is experiencing a sign/symptom that he/she would associate with hypoglycemia or a blood glucose measurement less than 3.5 mmol/L (63 mg/dL).

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Table 14. Listing of Severe Hypoglycemic Episodes, All Entered Patients

Patient	Previous Insulin Pen Experience?	Visit	Severe[a]	BG Level (mmol/L)	Able to Treat Self?	Food or Drink as Treatment?	Receive a Glucagon Injection?	Receive IV Glucose Injection?	Result in Coma?	Related to PPB?
1	Yes	2	Yes	6.6	No	Yes	No	No	No	No
2	Yes	2	Yes	7.7	No	Yes	No	No	No	No
3	Yes	2	Yes	3.0	No	Yes	No	No	No	No
		2	Yes	3.4	No	Yes	No	No	No	No
		2	Yes	3.1	No	Yes	No	No	No	No
		3	Yes	3.5	No	Yes	No	No	No	No
4	Yes	3	Yes	4.6	No	Yes	No	No	No	No

Abbreviation: - = no value taken by patient; BG = blood glucose; IV = intravenous; PPB = Prefilled Pen B.

a Severe hypoglycemia was defined as hypoglycemia where the patient required assistance from another person and which was associated with either a blood glucose level less than 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

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Table 15. Listing of Prefilled Pen B-Related Hypoglycemic Episodes, All Entered Patients

Patient	Previous Insulin Pen Experience?	Visit	Severe[a]	BG Level (mmol/L)	Able to Treat Self?	Food or Drink as Treatment?	Receive a Glucagon Injection?	Receive IV Glucose Injection?	Result in Coma?	Related to PPB?
5	Yes	2	No	5.7	Yes	Yes	No	No	No	Yes
		2	No	5.8	Yes	Yes	No	No	No	Yes
		2	No	5.4	Yes	Yes	No	No	No	Yes
		2	No	5.6	Yes	Yes	No	No	No	Yes
		2	No	4.9	Yes	Yes	No	No	No	Yes
6	Yes	3	No	3.6	Yes	Yes	No	No	No	Yes
7	Yes	2	No	2.6	Yes	Yes	No	No	No	Yes
		2	No	2.8	Yes	Yes	No	No	No	Yes
		2	No	2.9	Yes	Yes	No	No	No	Yes
		2	No	2.8	Yes	Yes	No	No	No	Yes
		2	No	2.7	Yes	Yes	No	No	No	Yes
		2	No	2.7	Yes	Yes	No	No	No	Yes
		2	No	3.3	Yes	Yes	No	No	No	Yes
8	Yes	2	No	2.5	Yes	Yes	No	No	No	Yes
		2	No	2.5	Yes	Yes	No	No	No	Yes
		2	No	2.7	Yes	Yes	No	No	No	Yes
		2	No	3.4	Yes	Yes	No	No	No	Yes
		2	No	2.9	Yes	Yes	No	No	No	Yes
		2	No	2.7	Yes	Yes	No	No	No	Yes
		2	No	3.2	Yes	Yes	No	No	No	Yes
		2	No	3.4	Yes	Yes	No	No	No	Yes
		2	No	3.2	Yes	Yes	No	No	No	Yes
		2	No	2.9	Yes	Yes	No	No	No	Yes
		2	No	3.3	Yes	Yes	U	U	U	Yes
		2	No	3.4	Yes	Yes	No	No	No	Yes

Abbreviations: BG = blood glucose; IV = intravenous; PPB = Prefilled Pen B; U = unknown.

a Severe hypoglycemia was defined as hypoglycemia where the patient required assistance from another person and which was associated with either a blood glucose level less than 2.8 mmol/L (50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

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Table 16. Listing of All Reported Prefilled Pen B-Related Hyperglycemic Episodes

Patient	Visit	Event Preferred Term	Duration Days	Event Severity	Serious Criteria?
9	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
	3	Hyperglycemia	1	Mild	No
10	2	Hyperglycemia	1	Moderate	No
	2	Hyperglycemia	11	Moderate	No
	2	Hyperglycemia	1	Moderate	No
	2	Hyperglycemia	11	Moderate	No
11	3	Hyperglycemia	1	Mild	No

Abbreviation: PPB = Prefilled Pen B

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Table 17. Listing of All Serious Adverse Events (Preferred Term), All Entered Patients (N = 370)

Patient	Visit	Event Preferred Term	Duration Days	Event Severity	Serious Criteria	Event Outcome	Related[a] to Study Procedure	Related[a] to Study Condition	Related[a] to Study Drug	Related[a] to Study Device
12	3	Chest discomfort	3	Moderate	HO	RR	No	No	No	No
13	2	Gastroenteritis	2	Mild	HO	RR	No	No	No	No
	3	Syncope	2	Moderate	HO	RR	No	No	No	No

Abbreviations: HO = hospitalized; PPB = Prefilled Pen B; RR = recovered/resolved.

[a] In the opinion of the investigator.

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Table 18. Listing of Discontinuations Due to Adverse Events or Death

Pat	Study Device	Visit	Event Preferred Term	Duration Days	Event Severity	Serious Criteria	Reason for Discontinuation	Event Outcome	Related[a] to Study Procedure	Related[a] to Study Condition	Related[a] to Study Drug	Related[a] to Study Device
10	PPB	1	Biliary cirrhosis primary	_	Mild	No	Adverse Event	NRR	No	No	No	No
			Hypercholesterolemia	_	Mild	No	Adverse Event	NRR	No	Yes	No	No
		2	Hyperglycemia	1	Moderate	No	Adverse Event	RR	No	No	No	Yes
				1	Moderate	No	Adverse Event	RR	No	No	No	Yes
				1	Moderate	No	Adverse Event	RR	No	No	No	Yes
				1	Moderate	No	Adverse Event	RR	No	No	No	Yes

Abbreviations: – = unknown; NRR = not recovered/not resolved; Pat = patient; PPB = Prefilled Pen B; RR = recovered/resolved.

[a] In the opinion of the investigator.

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Table 19. Treatment-Emergent Adverse Events Occurring in Greater Than or Equal to 2% of Patients, All Patients Who Used the Prefilled Pen B at Least Once

Event Classification (Preferred Term)	Prior insulin pen experience	No prior insulin pen experience	Total N (%)
Hypoglycemia	9 (3.6)	6 (6.5)	15 (4.4%)
Nasopharyngitis	9 (3.6)	2 (2.2)	11 (3.2%)

Abbreviation: N = number.

Table 20. Summary of Exposure to Prefilled Pen B

Duration of Exposure (weeks)	n (%)
< 4	13 (3.80)
>=4 and < 8	90 (26.32)
>= 8	229(66.96)

Mean Weeks: 7.96
Total Patient-Weeks: 2642.57
Standard Deviation: 1.59

Abbreviation: n = total number of patients within the specified category.

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Laboratory Values

The mean fasting plasma glucose value was 9.9 mmol/L (PIPE: 9.9 mmol/L, NPIPE: 9.6 mmol/L) at baseline and 9.0 mmol/L (PIPE: 9.1 mmol/L, NPIPE: 8.8 mmol/L) at endpoint (Table 21 and Table 22).

Table 21. Summary and Analysis of Fasting Blood Glucose Values and Change from Baseline by Visit, All Patients Who Used the Prefilled Pen B at Least Once

Descriptive Statistics	Visit: Baseline	2	3	Endpoint(LOCF)	p-value*
Actual Measurement					<0.001
Number of Patients	338	338	338	338	
Mean	9.86	8.88	8.31	8.99	
Median	9.50	8.85	8.50	8.70	
Maximum	26.60	22.10	20.40	20.40	
Minimum	0.00	0.00	0.00	0.00	
Standard Deviation	3.78	4.10	4.28	3.65	
Standard Error Mean	0.21	0.22	0.23	0.20	
Change from Baseline					0.178
Number of Patients	----	338	338	338	
Mean	----	-0.97	-1.55	-0.87	
Median	----	-0.55	-0.80	-0.60	
Maximum	----	15.70	16.80	16.80	
Minimum	----	-26.60	-26.60	-26.60	
Standard Deviation	----	4.97	5.43	4.87	
Standard Error Mean	----	0.27	0.30	0.26	

Abbreviation: LOCF = last observation carried forward.

*p-values were obtained from analysis of variance (ANOVA) model with visit.

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Table 22. Summary and Analysis of Fasting Plasma Glucose (mmol/L) and Change from Baseline, by Visit; Comparison of Prior Insulin Pen Experience

Prior Insulin Pen Experience	Descriptive Statistics	Visit(Weeks) Baseline	2(4)	3(8)	Endpoint(LOCF)
No	Actual Measurement				
	Number of Patients	89	89	89	89
	Mean	9.64	8.41	8.35	8.77
	Median	9.50	8.20	8.40	8.50
	Maximum	20.70	16.70	18.40	18.40
	Minimum	0.00	0.00	0.00	0.00
	Standard Deviation	3.68	3.98	4.12	3.79
	Standard Error Mean	0.39	0.42	0.44	0.40
	Change from Baseline				
	Number of Patients	----	89	89	89
	Mean	----	-1.23	-1.29	-0.87
	Median	----	-0.70	-0.50	-0.50
	Maximum	----	11.00	9.00	9.00
	Minimum	----	-16.00	-16.90	-16.00
	Standard Deviation	----	4.74	5.01	4.39
	Standard Error Mean	----	0.50	0.53	0.47
Yes	Actual Measurement				
	Number of Patients	249	249	249	249
	Mean	9.93	9.05	8.29	9.06
	Median	9.50	9.10	8.60	8.80
	Maximum	26.60	22.10	20.40	20.40
	Minimum	0.00	0.00	0.00	0.00
	Standard Deviation	3.81	4.14	4.34	3.60
	Standard Error Mean	0.24	0.26	0.28	0.23
	Change from Baseline				
	Number of Patients	----	249	249	249
	Mean	----	-0.88	-1.64	-0.87
	Median	----	-0.50	-0.90	-0.60
	Maximum	----	15.70	16.80	16.80
	Minimum	----	-26.60	-26.60	-26.60
	Standard Deviation	----	5.05	5.58	5.04
	Standard Error Mean	----	0.32	0.35	0.32
Prior Insulin Pen Experience Comparison (p-value*)					
Actual Measurement		0.530	0.207	0.910	0.512
Change from Baseline			0.574	0.599	0.997

Abbreviation: LOCF = last observation carried forward.

*p-values were obtained from analysis of variance (ANOVA) model with Prior Insulin Pen Experience.

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