Appendix G

Summary of Clinical Trials

8.D Controlled clinical studies

8.D.1 Table of all controlled studies

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase III, type 1 diabetes										
HOE 901/3001 **Report:** *8:v1.161:p013* **Quality of life Report:** *8:v1.200:p001* **CRFs:** N21081/CRF/3001 **Tabulations:** *Appendix C, 8:v1.172:p247* Multicenter Multinational 63 sites Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Netherlands, Norway, Sweden, Switzerland, UK F1998CLN0001	Complete (21Aug97 - 13Aug98)	Open-label, parallel group, stratified by center, randomized, active-controlled 28 weeks	Total: 585 Sex: 326M/259F Age Range: 17 - 77 yrs Mean±SD: 39.2 ± 11.89 yrs Race: White 579/585 Black 3/585 Asian/Oriental 1/585 Other 2/585	Type 1 diabetic subjects >1 year insulin treatment C-peptide <0.5 nmol/L GHb ≤12.0% 18-80 years	HOE 901 once daily at bedtime, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 292 Permanently discontinued: 16	NPH once or twice daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 293 Permanently discontinued: 21	**Efficacy:** Primary: GHb Secondary: Hypoglycemia; fasting glucose (FPG; SMBG); nocturnal blood glucose; 24-hour blood glucose profile; variability of fasting glucose Other: Insulin dose **Safety:** Adverse events (including serious hypoglycemia and local tolerance at injection site); standard clinical chemistry and clinical hematology; insulin antibodies; *E. coli* protein antibodies; ophthalmological examination; fundus photography; ECG **Quality of life:** DTSQ; W-BQ	HOE 901 provided a level of glycemic control that was at least as effective as NPH. Overall, HOE 901 did not significantly change GHb, FPG, or FBG compared to NPH. However, there appeared to be an advantage for subjects with a prior basal insulin regimen of more than once daily who received HOE 901, as these subjects had a clinically relevant decrease in FBG compared to those who received NPH. The frequency of hypoglycemic events was not significantly different between the 2 treatment groups, but there was better control of the nocturnal glucose level with HOE 901 compared to NPH.	**Total:** 377/585 (64.4%) **HOE 901:** 192/292 (65.8%) **NPH:** 185/293 (63.1%)	HOE 901 HMR, Germany No. 30 11Dec96

8:v1.161:p002

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase III, type 1 diabetes (cont.)										
HOE 901/3004 **Report:** 8:v1.207:p001 **Quality of life report:** 8:v1.245:p001 **CRFs:** N21081/CRF/3004 **Tabulations:** *Appendix C,* 8:v1.217:p265 Multicenter 49 sites[c] USA K1998CLN0001	Complete (25Jun97 - 23Jun98)	Open-label, parallel group, stratified by center and prior basal regimen, randomized, active-controlled 28 weeks	Total: 534 Sex: 270M/264F Age Range: 18 - 74 yrs Mean±SD: 38.5±12.04 yrs Race: White 509/534 Black 19/534 Asian/Oriental 4/534 Other 2/534	Type 1 diabetic subjects Daily insulin for at least 1 year Postprandial C-peptide ≤0.5 nmol/L GHb ≤12.0% 18-80 years	HOE 901 once daily at bedtime, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 264 Permanently discontinued: 31	NPH once or twice daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 270 Permanently discontinued: 22	**Efficacy:** Primary: GHb Secondary: Hypoglycemia; fasting glucose (FPG; SMBG); 24-hour plasma glucose profile; variability of fasting glucose Other: Insulin dose **Safety:** Adverse events (including serious hypoglycemia and local tolerance at injection site); standard clinical chemistry and clinical hematology; insulin antibodies; *E. coli* protein antibodies; ophthalmological examination; fundus photographs; ECG **Quality of life:** DTSQ; W-BQ	HOE 901 was as effective as NPH in maintaining good glycemic control. HOE 901 did not significantly change GHb, but did significantly decrease fasting FPG, compared to NPH. Better FBG control was attained with a lower dose of HOE 901 than with NPH. A higher percentage of subjects achieved the target blood glucose level of <6.6 mmol/L with HOE 901 than with NPH. HOE 901 was as effective as NPH in maintaining good glycemic control in subgroups of subjects with a prior basal insulin regimen of more than once daily insulin. HOE 901 subjects had a lower frequency of symptomatic, nocturnal, and severe hypoglycemic events compared to NPH. Significantly fewer HOE 901 subjects that had a prior once daily basal insulin regimen experienced nocturnal hypoglycemia compared to NPH. The occurrence of adverse events was similar in both treatment groups. The HOE 901 treatment group had more reports of injection site pain, possibly due to the pH of the solution. There was no evidence of a greater immunogenic response to HOE 901 compared to NPH.	**Total:** 457/534 (85.6%) **HOE 901:** 223/264 (84.5%) **NPH:** 234/270 (86.7%)	HOE 901 HMR, Germany No. 29 12Dec96

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase III, type 1 diabetes (cont.)										
HOE 901/3005 **Report:** 8:v1.252:p001 **CRFs:** N21081/CRF/3005 **Tabulations:** *Appendix C,* 8:v1.262:p242 Multicenter Multinational 60 sites[c] USA, Canada K1998CLN0003	Complete (27Oct97 - 31Jul98)	Open-label, parallel group, stratified by center and prior basal regimen, randomized, active-controlled 16 weeks	Total: 619 Sex: 313M/306F Age Range: 18 - 80 yrs Mean±SD: 39.2±12.16 yrs Race: White 600/619 Black 16/619 Asian/Oriental 0/619 Other 3/619	Type 1 diabetic subjects Daily insulin for at least 1 year and NPH and Lispro for 3 months C-peptide ≤0.5 nmol/L GHb ≤12.0% 18-80 yrs	HOE 901 once daily, individually titrated, plus insulin lispro injections before meals, individually titrated Total exposed: 310 Permanently discontinued: 15	NPH once or twice daily, individually titrated, plus insulin lispro injections before meals, individually titrated Total exposed: 309 Permanently discontinued: 16	**Efficacy:** Primary: GHb Secondary: Hypoglycemia; fasting glucose (FPG, SMBG); 24-hour plasma glucose profile; variability of fasting glucose Other: Insulin dose **Safety:** Adverse events (including serious hypoglycemia and local tolerance at injection site); standard clinical chemistry and clinical hematology; insulin antibodies; *E. coli* protein antibodies; ECG	HOE 901 was as effective as NPH in maintaining good glycemic control. At study endpoint, HOE 901 subjects had significantly decreased FPG and FBG compared to NPH. Better FBG control was attained with a lower dose of HOE 901 than with NPH. A higher percentage of subjects achieved the target blood glucose level of <6.6 mmol/L with HOE 901 than with NPH. HOE 901 was as effective as NPH in maintaining good glycemic control in subgroups of subjects with a prior basal insulin regimen of more than once daily insulin. The frequency of symptomatic, nocturnal, and severe hypoglycemic events was not significantly different between treatment groups when summarized by prior basal insulin regimen. The occurrence of adverse events was similar in both treatment groups. The HOE 901 treatment group had more reports of injection site pain, possibly due to the pH of the solution. There was no evidence of a greater immunogenic response to HOE 901 compared to NPH.	**Total:** 486/619 (78.5%) **HOE 901:** 250/310 (80.6%) **NPH:** 236/309 (76.4%)	HOE 901 HMR, Germany No. 29 12Dec96

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase III, type 2 diabetes										
HOE 901/3006 **Report:** *8:v1.288:p002* **Quality of life Report:** *8:v1.321:p001* **CRFs:** N21081/CRF/3006 **Tabulations:** *Appendix C, 8:v1.298:p089* Multicenter 59 sites[c] USA K1998CLN0004	Complete (27Jul97 - 22Oct98)	Open-label, parallel group, stratified by center and prior basal regimen, randomized, active-controlled 28 weeks	Total: 518 Sex: 311M/207F Age Range: 35 - 80 yrs Mean±SD: 59.3±9.81 yrs Race: White 417/518 Black 76/518 Asian/Oriental 17/518 Other 7/518	Type 2 diabetic subjects Currently treated with insulin for at least 3 months prior GHb 7.0 - 12.0% BMI <40 kg/m^2 40-80 yrs	HOE 901 once daily, individually titrated, with or without regular insulin injections before meals, individually titrated Total exposed: 259 Permanently discontinued: 28	NPH once or twice daily, individually titrated, with or without regular insulin injections before meals, individually titrated Total exposed: 259 Permanently discontinued: 21	**Efficacy:** Primary: GHb Secondary: Hypoglycemia; fasting glucose (FPG, SMBG); variability of fasting glucose; fasting serum C-peptide; fasting serum insulin Other: Insulin dose **Safety:** Adverse events (including serious hypoglycemia and local tolerance at injection site); standard clinical chemistry and clinical hematology; insulin antibodies; *E. coli* protein antibodies; opthalmological examination; fundus photographs; ECG **Quality of life:** DTSQ; W-BQ	HOE 901 was as effective as once or twice daily NPH in providing and maintaining good glycemic control in type 2 diabetic subjects. The HOE 901 treatment group had a significantly lower frequency of nocturnal hypoglycemia from month 2 to the end of the study and over the entire treatment phase compared with the NPH treatment group. The frequency of all symptomatic hypoglycemic events was similar between treatment groups. Overall, the occurrence of adverse events was similar in the HOE 901 and NPH treatment groups.	**Total:** 436/518 (84.2%) **HOE 901:** 218/259 (84.2%) **NPH:** 218/259 (84.2%)	HOE 901 HMR, Germany No. 29 12Dec96

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase III, type 2 diabetes (cont.)										
HOE 901/3002 **Report:** *8:v1.327:p001* **CRFs:** N21081/CRF/3002 **Tabulations:** *Appendix C, 8:v1.339:p274* Multicenter Multinational 57 sites Austria, Croatia, Czech Republic, Denmark, Finland, Germany, Italy, Netherlands, Norway, Slovenia, South Africa, Spain, Sweden, Switzerland, UK F1998CLN0003	Ongoing Interim report (17Sep97 – 19Aug98)	Open-label, parallel group, stratified by center, randomized, active-controlled 20 weeks (interim analysis) 52 weeks (final analysis)	Total: 570 Sex: 306M/264F Age Range: 34 – 80 yrs Mean±SD: 59.5±9.21 yrs Race: White 529/570 Black 23/570 Asian/Oriental 12/570 Other 6/570	Type 2 diabetic subjects Previous OAD treatment at least 1 yr; treatment inadequacy for at least 3 months with OADs or with an insulin once daily/SU combination GHb 7.5% - 12.0% BMI <40kg/m^2 40-80 yrs	HOE 901 once daily at bedtime, individually titrated, combined with OAD according to the subject's previous habits Total exposed: 289 Permanently discontinued: 8	NPH once daily at bedtime, individually titrated, combined with OAD according to the subject's previous habits Total exposed: 281 Permanently discontinued: 17	**Efficacy:** Primary: GHb Secondary: Hypoglycemia; fasting glucose (FPG; SMBG); nocturnal blood glucose; 24-hr blood glucose profile; variability of fasting blood glucose; fasting serum C-peptide; fasting serum insulin Other: Insulin dose **Safety:** Adverse events (including serious hypoglycemia and local tolerance at injection site); standard clinical chemistry and clinical hematology; insulin antibodies; *E. coli* protein antibodies; ophthalmological examination	The results of this study show that HOE 901 provides a level of glycemic control that is at least as effective as NPH. Overall, HOE 901 did not significantly change either GHb, FPG, or FBG compared to NPH. However, a clinically relevant difference between treatment groups was observed in the analysis of nocturnal hypoglycemia throughout the entire treatment phase where more NPH subjects experienced at least 1 episode of nocturnal hypoglycemia. This difference between groups was even larger in the subgroup of insulin-naïve subjects.	**Total:** 263/570 (46.1%) **HOE 901:** 125/289 (43.3%) **NPH:** 138/281 (49.1%)	HOE 901 HMR, Germany No. 30 11Dec96

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Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase II, type 1 diabetes										
HOE 901/2002 **Report:** 8:v1.354:p002 **CRFs:** No case report forms are provided for this study **Tabulations:** *Appendix I.A.1,* 8:v1.359:p173 through *Appendix I.B.26* Multicenter 32 sites USA B1998CLN0001 *Diabetes* 1998; 47 (suppl 1): A92 *Diabetes* 1998; 47 (suppl 1): A359 16th IDF Cong Satellite Symp, Helsinki (Jul 1997) in: Abstracts, 1997, p. 48	Complete (01Feb96 - 05Jun96)	Open (HOE 901 versus NPH) and partially double-blind (formulations of HOE 901), parallel group, stratified by center, randomized, active-controlled 4 weeks	Total: 256 Sex: 133M/123F Age Range: 18 - 68 yrs Mean±SD: 37.5±11.86 yr Race: White 240/256 Black 1/256 Asian/Oriental 2/256 Other 13/256	Type 1 diabetic subjects Previous basal-bolus insulin treatment for at least 2 months HbA_{1c}≤10% BMI 18-28 kg/m^2 18-70 yrs	HOE 901 once daily, individually titrated, plus regular insulin injections before meals, individually titrated HOE 901 [80] once daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 168 Permanently discontinued: 0	NPH once or twice daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 88 Permanently discontinued: 1	**Efficacy:** Primary: FPG at endpoint Secondary: FBG; blood glucose profile; nocturnal blood glucose; stability of FPG and FBG; fasting serum insulin; insulin dose; hypoglycemia; HbA_{1c}; fructosamine; serial overnight plasma glucose (subgroup of subjects) **Safety:** Adverse events (including injection site reactions); standard hematology and blood chemistry; insulin antibodies; *E. coli* protein antibodies; vital signs; physical examination; ECG	HOE 901 once daily had a more favorable benefit-to-risk assessment than NPH insulin once or twice daily. HOE 901 was clinically and significantly more effective than NPH in lowering FPG. The HOE 901 [80] formulation was not better than the HOE 901 [30] formulation. All 3 insulin formulations were well-tolerated.	**Total:** 146/256 (57.0%) **HOE 901** 101/168 (60.1%) **NPH:** 45/88 (51.1%)	HOE 901 HMR No. 26 13Nov95 HOE 901[80] HMR No. 25 13Nov95

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Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase II, type 1 diabetes (cont.)										
HOE 901/2003 **Report:** 8:v1.371:p001 **CRFs:** N21081/CRF/2003 **Tabulations:** *Appendix I.1,* 8:v1.378:p125 through *Appendix I.4.7* Multicenter Multinational 42 sites Austria, Denmark, Finland, France, Germany, Netherlands, Norway, Sweden, Switzerland F1998CLN0010 *Diabetes* 1998; 47 (suppl 1): A62 *Diabetologia* 1998; 41 (suppl 1): A49 16th IDF Cong Satellite Symp, Helsinki (Jul 1997) in: Abstracts, 1997, p. 48	Complete (20Dec95 - 06Aug96)	Open (HOE 901 versus NPH) and partially double-blind (formulations of HOE 901), parallel group, stratified by center, randomized, active-controlled 4 weeks	Total: 333 Sex: 203M/130F Age Range: 18 - 70 yrs Mean±SD: 36.3±11.4 yrs Race: White 326/333 Black 2/333 Asian/Oriental 2/333 Other 3/333	Type 1 diabetic subjects Previous basal-bolus insulin treatment for at least 2 months $HbA_{1c} \leq 10\%$ BMI 18-28 kg/m^2 18-70 yrs	HOE 901 once daily, individually titrated, plus regular insulin injections before meals, individually titrated HOE 901 [80] once daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 223 Permanently discontinued: 7	NPH once or twice daily, individually titrated, plus regular insulin injections before meals, individually titrated Total exposed: 110 Permanently discontinued: 5	**Efficacy:** Primary: FPG at endpoint Secondary: FBG; blood glucose profile; nocturnal blood glucose; stability of FBG; treatment response; fasting serum insulin; insulin dose; hypoglycemia; HbA_{1c}; fructosamine **Safety:** Adverse events (including serious hypoglycemia and local tolerance by inspection); standard hematology and clinical chemistry; lipid profile; insulin antibodies; *E. coli* protein antibodies; vital signs; physical examination **Quality of life:** W-BQ and DTSQ	HOE 901 administered once daily at bedtime as a basal insulin in type 1 diabetic subjects is more effective than NPH once or twice daily and is generally at least as safe as NPH. There is a possible safety improvement over NPH once daily in terms of nocturnal hypoglycemia. HOE 901 [30] and HOE 901 [80] appear to be equally good candidates for use in the Phase III clinical trial program.	**Total:** 152/333 (45.6%) **HOE 901** 100/223 (44.8%) **NPH** 52/110 (47.3%)	HOE 901 Hoechst AG No. 22 21Mar95 HOE 901[80] Hoechst AG No. 23 22Mar95

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase II, type 2 diabetes										
HOE 901/2004 **Report:** 8:v1.394:p002 **CRFs:** N21081/CRF/2004 **Tabulations:** *Appendix I.1,* 8:v1.403:p002 through *Appendix I.4.6* Multicenter Multinational 29 sites Austria, Czech Republic, Denmark, Finland, Germany, Netherlands, Norway, South Africa, Sweden, UK F1998CLN0011 *Diabetologia* 1998; 41 (suppl 1): A245, abs 948 *Diabetes* 1998; 47 (suppl 1): A101 16th IDF Cong Satellite Symp, Helsinki (Jul 1997) in: Abstracts, 1997, p. 48	Complete (18Dec95 - 07Jun96)	Open (HOE 901 versus NPH) and partially double-blind (formulations of HOE 901), parallel group, stratified by center, randomized, active-controlled 4 weeks	Total: 204 Sex: 122M/82F Age Range: 29 – 78 yrs Mean±SD: 59.4±10.61 yrs Race: White 180/204 Black 5/204 Asian/Orlental 7/204 Other 12/204	Type 2 diabetic subjects Previous treatment with sulphonyl-urea alone or in combination with metformin and/or acarbose; maximum dose of sulphonyl-urea for at least 3 months HbA_{1c}≥7% BMI 21-35 kg/m^2 40-80 yrs	HOE 901 once daily, individually titrated, plus oral antidiabetic drugs as previously prescribed HOE 901 [80] once daily, individually titrated, plus oral antidiabetic drugs as previously prescribed Total exposed: 136 Permanently discontinued: 2	NPH once or twice daily, individually titrated, plus oral antidiabetic drugs as previously prescribed Total exposed: 68 Permanently discontinued: 0	**Efficacy:** Primary: FPG at endpoint Secondary: FBG; blood glucose profile; nocturnal blood glucose; stability of FBG; treatment response; fasting serum insulin; fasting serum C-peptide; insulin dose; hypoglycemia; HbA_{1c}; fructosamine; non-esterified fatty acids **Safety:** Adverse events (including serious symptomatic hypoglycemia and local tolerance by inspection); standard hematology and clinical chemistry; lipid profile; insulin antibodies; *E. coli* protein antibodies; vital signs; physical examination	HOE 901 may have a favorable benefit-to-risk assessment compared with NPH in type 2 diabetic subjects when administered together with a sulphonylurea alone or in combination with metformin and/or acarbose. HOE 901 was equally as well tolerated as NPH, was as effective in lowering FPG, and was associated with less nocturnal hypoglycemia. No differences were detected between HOE 901 formulations in the primary and secondary efficacy variables; there were no safety concerns of clinical relevance. HOE 901 [30] was selected for use in the Phase III clinical trial program.	**Total:** 60/204 (29.4%) **HOE 901** 47/136 (34.6%) **NPH** 13/68 (19.1%)	HOE 901 Hoechst AG No. 22 21Mar95 HOE 901 Hoechst Ag No. 28 05Dec95 HOE 901 [80] Hoechst AG No. 23 22Mar95 HOE 901 [80] Hoechst AG No. 27 06Dec95

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase II, type 2 diabetes (cont.)										
HOE 901/2005 **Report:** *8:v1.413:p001* **CRFs:** N21081/CRF/2005 **Tabulations:** *Appendix I.A.1,* *8:v1.417:p209* through *Appendix I.B.25* Multicenter 26 sites USA B1998CLN0002 *Diabetes* 1998; 47 (suppl 1): A103 16th IDF Cong Satellite Symp, Helsinki (Jul 1997) in: Abstracts, 1997, p. 48	Complete (15Feb96 - 10Jul96)	Open (HOE 901 versus NPH) and partially double-blind (formulations of HOE 901), parallel group, stratified by center, randomized, active-controlled 4 weeks	Total: 157 Sex: 102M/55F Age Range: 28 - 79 yrs Mean±SD: 57.4±10.36 yr Race: White 118/157 Black 18/157 Asian/Oriental 2/157 Other 19/157	Type 2 diabetic subjects Suboptimal treatment with maximal SU or SU plus metformin doses No insulin monotherapy for 1 month prior; no chronic insulin treatment for 6 months prior. FPG ≤250 mg/dL (13.9 mmol/L) HbA_{1c} ≥7% BMI 21-36 kg/m^2 35-80 yrs	HOE 901 once daily, individually titrated HOE 901 [80] once daily, individually titrated Total exposed: 108 Permanently discontinued: 1	NPH once daily, individually titrated Total exposed: 49 Permanently discontinued: 2	**Efficacy:** Primary: FPG at endpoint Secondary: FBG; blood glucose profile; nocturnal blood glucose; stability of FPG and FBG; fasting serum insulin; C-peptide; insulin dose; hypoglycemia; HbA_{1c}; fructosamine **Safety:** Adverse events (including injection site reactions); standard hematology and blood chemistry; insulin antibodies; *E. coli* protein antibodies; vital signs; physical examination; ECG	All 3 insulins produced similar, significant, clinically meaningful reductions from baseline FPG. All 3 insulins were well-tolerated.	**Total:** 88/157 (56.1%) **HOE 901** 56/108 (51.9%) **NPH** 32/49 (65.3%)	HOE 901 HMR No. 26 13Nov95 HOE 901 [80] HMR No. 25 13Nov95

Table 8-16 Table of all controlled studies

Study number Dossier Location Center(s) Report No. Publications	Status (Start date/ Completion date)	Design Duration of treatment	Baseline demographics	Diagnosis & criteria for inclusion	Dose (No. exposed each treatment) Route and dosage form HOE 901[a]	Comparator	Criteria for evaluation	Results/ Conclusions	Total No. of subjects with TEAEs/Total No. of treated subjects[b] (Percentage)	Plant Lot No. Date of manufacture
Phase II, type 2 diabetes (cont.)										
HOE 901/2006 **Report:** 8:v1.425:p001 **CRFs:** N21081/CRF/2006 **Tabulations:** *Appendix I.1,* 8:v1.428:p120 through *Appendix I.4.6* Multicenter Multinational 11 sites Austria, Finland, Germany, Netherlands, Sweden F1997CLN0003	Complete (12Mar96 - 19Aug96)	Open-label, parallel group, stratified by center, randomized, active-controlled 4 weeks	Total: 114 Sex: 68M/46F Age Range: 32 – 78 yrs Mean±SD: 60.7±10.25 yrs Race: White 111/114 Black 0/114 Asian/Oriental 3/114 Other 0/114	Type 2 diabetic subjects Previous insulin treatment once or twice daily for at least 2 months HbA_{1c} 7.5% - 12.0% BMI 21-32 kg/m^2 40-80 yrs	HOE 901 once daily, individually titrated plus regular insulin injections before meals, individually titrated Total exposed: 57 Permanently discontinued: 3	One or 2 injections daily of subject's prior insulin (NPH or mixed insulin), individually titrated plus regular insulin injections before meals, individually titrated Total exposed: 57 Permanently discontinued: 3	**Efficacy:** Primary: FPG at endpoint Secondary: FBG; blood glucose profile; nocturnal blood glucose; stability of FBG; fasting serum insulin; fasting serum C-peptide; insulin dose; hypoglycemia; HbA_{1c}; fructosamine; non-esterified fatty acids **Safety:** Adverse events (including serious symptomatic hypoglycemia and local tolerance by inspection); standard hematology and clinical chemistry; lipid profile; insulin antibodies; *E. coli* protein antibodies; vital signs; physical examination	An intensified regimen of HOE 901 [30] plus regular human insulin can be introduced without any additional risk in type 2 diabetic subjects previously on conventional insulin treatment. Results indicated that HOE 901 [30] plus regular insulin is at least as effective as conventional treatment. Overall there was a tendency towards improvement in the HOE 901 group but the study was too short to show consistently significant differences.	**Total:** 42/114 (36.8%) **HOE 901** 22/57 (38.6%) **Continued prior insulin** 20/57 (35.1%)	HOE 901 Hoechst AG No. 28 06Dec95

TEAE = treatment-emergent adverse event; M = male; F = female; SD = standard deviation; OAD = oral antidiabetic drug; SU = sulfonylurea; BMI = body mass index
NOTE: This table includes data from all subjects randomized and treated in each study.

[a] Numbers in square brackets refer to the zinc concentration of the HOE 901 formulations, e.g., HOE 901 [80] = HOE 901 with 80 µg/mL zinc. HOE 901 refers to the standard formulation with 30 µg/mL zinc.

[b] For purposes of the integrated safety database, a consistent methodology was utilized across all studies to assign adverse events to a specific treatment as well as to classify adverse events as treatment emergent or non-treatment emergent. This classification methodology may have differed from that utilized in the individual Phase I and II study reports. Therefore, the number of adverse events assigned to a specific treatment or classified as treatment emergent may differ between the individual study reports and the integrated safety database.

[c] One additional site in studies 3004 (site 17) and 3005 (site 156), two additional sites in study 3006 (sites 67 and 86), and three additional sites in studies 2003 (sites 29, 30, and 47) and 3002 (sites 3202, 3229 and 3230) received drug but enrolled no subjects.

Contact Tracking/FDA Review
All Corresp/Submission/Contacts To/From FDA
Product History Log From 01/01/95 To 10/22/99
HOE 901 (INSULIN ANA
IND Number 49,078

Submission Date	Log Number IND/NDA:Date	Origin/ Type	Classi- fication	Supp/ Serial#	Description/ Comments
95/08/22	49,078:950822	MMD Fax	Other		FAX:JLD/JSHORT PRE-IND MTG REQ/ FAX FROM JDEMARTINO TO JSHORT REQUESTING A PRE-IND MEETING FOR HOE-901. (NEW JERSEY) (SEE 1996 GENERAL CORRESPONDENCE FILE FOLDER) KML
95/08/23	49,078:950823	MMD Fax	Other		FAX:JLD/SLIN DIPYRONE MTG MIN/ FAX FROM JDEMARTINO TO SUE CHING LIN REGARDING DIPYRONE PRE-IND MEETING MINUTES. (NEW JERSEY) (DOCUMENT NEVER RECEIVED FROM NEW JERSEY) KML
95/08/25	49,078:950825	MMD Sub	Other		SUBMISSION OF AGENDA & OVERHDS/ SUBMISSION: HARD COPY OF PRE-IND AGENDA AND OVERHEAD TRANSPARENCIES. (NEW JERSEY) (HARD COPY NOT AVAILABLE-NEVER RECEIVED FROM NEW JERSEY) KML
95/08/29	49,078:950829	MMD Tel	Other		CONTACT:JLD/JSHORT PRE-IND MTG/ PHONE CONTACT BY JDEMARTINO TO JSHORT & CAUSTIN SETTING PRE-IND MEETING DATE FOR OCTOBER 24. (NEW JERSEY) (SEE 1996 GENERAL CORRESPONDENCE FILE FOLDER) KML
95/09/11	49,078:950911	MMD Sub	Other		SUBMISSION OF PRE-IND DOCUMENT/ SUBMISSION OF PRE-IND BRIEFING DOCUMENT FOR MEETING ON 10/24/95 WITH FDA. (NEW JERSEY) (COVER LETTER IN 96 GENERAL CORRESPONDENCE-FULL COPY IN DCC) KML
95/10/04	49,078:951004	MMD Tel	Other		CONTACT:JLD/JSHORT FDA ATTENDE/ PHONE CONTACT BY JDEMARTINO TO JSHORT WHO PROVIDED LIST OF FDA ATTENDEES AT PRE-IND MEETING. (NEW JERSEY) (SEE 1996 GENERAL CORRESPONDENCE FILE FOLDER) KML

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95/10/13	49,078:951013	MMD Tel	Other		CONTACT:JLD/JSHORT PRE-IND MTG/ PHONE CONTACT BETWEEN JDEMARTINO AND JSHORT REGARDING PRE-IND MEETING - PRE-SENTATIONS SHOULD BE BRIEF. (SEE 1996 GENERAL CORRESPONDENCE FILE FOLDER) KML
95/10/24	49,078:951024	MMD Mtg	Other		MEETING:PRE-IND MEETING MINUTE/ SPONSOR'S MINUTES FOR PRE-IND MEETING WITH FDA HELD ON 10/24. ALSO CONTAINS HARDCOPY OF SLIDES PRESENTED. (NEW JERSEY) (SEE 96 GENERAL CORRSP. FILE)KML
95/10/27	49,078:951027	MMD Fax	Other		FAX:JLD/JSHORT PRE-IND SLIDES/ FAX BY JDEMARTINO TO JSHORT COPY OF OVERHEADS PRESENTED AT PRE-IND MEETING ON 10/24. (NEW JERSEY) (SEE 1996 GENERAL CORRESPONDENCE FILE FOLDER) KML
95/11/10	49,078:951110	MMD Sub	Original	000	ORIGINAL IND SUBMISSION/ INITIAL SUBMISSION OF INVESTIGATIONAL NEW DRUG APPLICATION. (NEW JERSEY) LJG SEVENTEEN VOLUME SUBMISSION
95/11/14	49,078:951114	MMD Tel	ALL		CONTACT:JLD/JSHORT: # ASSIGNM./ FDA CONTACT REPORT - JLD & JOHN SHORT RE: IND NUMBER ASSIGNMENT. (NEW JERSEY) LJG
95/11/16	49,078:951116	FDA Ltr	ALL		FDA LTR:ACKNOW RECPT OF IND/ OFFICIAL LETTER FROM JOHN SHORT (FDA) ACKNOWLEDGING RECEIPT OF IND APPLICATION SUBMITTED WITH THE PROPER IDENTIFYING DATA. (NEW JERSEY) LJG
96/01/23	49,078:960123	MMD Sub	Other	001	LTR TO FDA: NAME CHANGE/ SUBMISSION: CORPORATE NAME CHANGE.

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96/01/30	49,078:960130	MMD Sub	Clinical	002	PROTOCOL AMENDMENT/ SUBMISSION - PROTOCOL AMENDMENT: CHANGE IN PROTOCOL 2005 (AMENDMENT A), NEW INVESTIGATORS FOR PROTOCOL 2002 AND 2005. (NEW JERSEY) LJG
	49,078:960130A	FDA Ltr	Other		MINUTES OF PRE-IND MEETING/ FDA'S MINUTES OF THE PRE-IND MEETING. (NEW JERSEY) LJG
96/02/16	49,078:960216	MMD Sub	Clinical	003	PROTOCOL AMENDMENT: NEW INVEST/ SUBMISSION: NEW INVESTIGATORS FOR PROTOCOLS 2002 & 2005. (NEW JERSEY) LJG
96/03/06	49,078:960306	MMD Sub	Clinical	004	PROTOCOL AMENDMENT: NEW INVEST/ SUBMISSION: NEW INVESTIGATORS FOR PROTOCOLS 2002 AND 2005. (NEW JERSEY) LJG
96/03/15	49,078:960315	MMD Sub	Clinical	005	PROTOCOL AMENDMENT: NEW INVEST/ SUBMISSION: NEW INVESTIGATORS FOR PROTOCOLS 2002 AND 2005. (NEW JERSEY) LJG
96/03/20	49,078:960320	MMD Sub	Clinical	006	PROTOCOL AMENDMENT: NEW INVEST/ SUBMISSION: NEW INVESTIGATORS FOR PROTOCOLS 2002 AND 2005. (NEW JERSEY) LJG
96/03/26	49,078:960326	FDA Tel	Other		CONTACT:JSHORT/JLD: NEW CSO/ NEW CSO (PROJECT MANAGER) FOR METABOLISM WILL BE JULIE RHEE. (NEW JERSEY) LJG
96/03/27	49,078:960327	MMD Sub	Clinical	007	PROTOCOL AMENDMENT: CHG IN PRO/ SUBMISSION: CHANGE IN PROTOCOL 2005 (AMENDMENT B). (NEW JERSEY) LJG

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96/04/15	49,078:960415	FDA Ltr	Clinical		REQUEST OF HMRI RE: 11/95 SUB/ LETTER TO JAMES L. DEMARTINO FROM FDA RELATIVE TO THEIR REVIEW OF 11/10/95 SUBMISSION, WITH RECOMMENDATIONS AND REQUEST FOR ADDITIONAL INFORMATION.
96/04/22	49,078:960422	MMD Sub	Clinical	008	PROTOCOL AMENDMENT: NEW INVEST/ NEW INVESTIGATORS PROTOCOL 2005 - JHEILEMAN, DMIKOLICH, SMILLER. NEW SUB FOR JROSENSTOCK. LMCCALL & MDUCKETT NO LONGER PARTICIPATING AS SUBS FOR STUDY CONDUCTED BYNSOLDER. ADDITIONAL CLINICAL LAB FOR STUDY BY DBELL. LJG
96/05/22	49,078:960522	MMD Sub	Clinical	009	NEW INVESTIGATORS, NEW SUB/ NEW INVESTIGATORS PROTOCOL 2005 - SHELDON BERGER, & JOHN HOLMES. NEW SUB-WILLIAM BROOKE FOR STUDY BY PAUL MOORE. LJG
96/06/18	49,078:960618	MMD Tel	Clinical		CNT: LPATTON/JRHEE/ GNT: LPATTON/JRHEE. LMP CONTACTED JULIE RHEE, EXPLAINED THAT SHE WAS THE NEW HMR CONTACT FOR HOE 901, AND ASKED WHETHER THE REQUEST FOR A MEETING HAD TO BE IN WRITING (IT DOES). REQUEST FAXED 6/19/96 (SEE 49,078:960619B).SEE CONTACT REPORT FOR LIST OF ITEMS REQUEST MUST INCLUDE.
96/06/19	49,078:960619	MMD Ltr	Clinical	010	GENERAL CORRESPONDENCE/ REQUEST A MEETING TO DISCUSS HOE 901, A RECOMBINANT HUMAN INSULIN ANALOGUE. THE PURPOSE OF THIS MEETING WILL BE TO UPDAT THE DIVISION ON THE PROGRESS OF THE DEVELOPMENT PROGRAM AND SPECIFICALLY TO GAIN GUIDANCE FROM THE DIVISION ON PLANS FOR THE PHASE III CLINICAL TRIALS.

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96/06/19	49,078:960619A	MMD Tel	Clinical		CNT: LPATTON/JRHEE (RE: S-010)/ CNT: LPATTON/JRHEE. LMP CALLED TO SAY SHE WAS FAXING THE REQUEST FOR MEETING LETTER. SHE ALSO DISCUSSED A STUDY DR. MISBIN HAD SUGGESTED BE CONDUCTED.
	49,078:960619B	MMD Fax	Clinical		FAX: LPATTON/JULIE RHEE/ FAX (TO BE FOLLOWED BY HARD COPY LETTER) SENT TO JRHEE REQUESTING A MEETING WITH THE DIVISION TO DISCUSS HOE 901. SEE LETTER (49,078:960619) AND CONTACT REPORT (49,078:960619A) FOR MORE DETAIL.
96/06/25	49,078:960625	FDA Tel	Clinical		CNT:JRHEE/LPATTON/ LTR:JRHEE/LPATTON. RHEE REQUESTED MORE INFORMATION ON THE MEETING WE ASKED FOR. PATTON PROMISED TO FAX A LETTER WITH THE ADDITIONAL INFO SOON. ON 6/28, J. RHEE CALLED AFTER RECEIVING LMP'S FAX. TENTA- TIVE MEETING DATE IS 8-8-96.
96/06/28	49,078:960628	MMD Sub	Clinical	011	GENERAL CORRESPONDENCE/ PURPOSE OF THIS GENERAL CORRESPONDENCE IS TO PROVIDE ADDITIONAL CLARITY ON SPECIFIC ISSUES HMR WOULD LIKE TO DISCUSS WITH THE DIVISION CONCERNING THE CLINICAL PROGRAM FOR HOE 901.
	49,078:960628A	MMD Fax	Clinical		LTR:LPATTON/SSOBEL/ FAX OF LTR:LPATTON/SSOBEL. LETTER ADDS CLARITY TO ISSUES HMR WANTS TO DISCUSS WITH THE DIV. OF METABOLISM AND ENDICRIN OLOGY DRUG PRODUCTS. ALSO MAILED LATER.
96/07/15	49,078:960715	MMD Tel	Clinical		CNT TO CONFIRM 8/8 MTG DATE/ SUMMARIZES SEVERAL PHONE CONTACTS WITH JULIE RHEE TO CONFIRM DATE OF MEETING TO DISCUSS THE CLINICAL DEVELOPMENT OF HOE 901. CONFIRMED MEETING DATE 8/8/96.

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96/07/15	49,078:960715A	FDA Fax	Clinical		MTG NOTICE FROM FDA FOR 8/8/96/ RECEIVED FAX FROM JULIE RHEE NOTIFYING DATE OF FDA MEETING: AUGUST 8, 1996, 10:00-11:00AM, PARKLAWN 3RD FLOOR, CONFERENCE ROOM "C". FDA ATTENDEES: SOLOMON SOBEL; GLORIA TREONDLE, ALEXANDER FLEMING, ROBERT MISBIN, DAN MARTICELLO, HAE-YOUNG AHN AND JULIE RHEE.
96/07/16	49,078:960716	MMD Sub	Clinical	012	PRE-MTG PKG/RESP. TO 4/15 LTR/ SUBMITTED PRE-MEETING PACKAGE FOR MEETING ON AUGUST 8, 1996, TO DISCUSS THE PHASE III CLINICAL DEVELOPMENT OF HOE 901. MMD ATTENDEES: RROSSKAMP, EBAADER, EDRAEGER, MHERZ, JSCHNEIDER, JZIMMERMAN, USHUKLA, AND LPATTON. RESPONSE TO 4-15-96 FDA LETTER & QUESTIONS FROM 10/24/95 MTG.
96/08/06	49,078:960806	FDA Tel	Clinical Pre-Clin		REQUEST:PHARMACOLOGY ON HOE901/ DR. RHEE OF FDA CALLED TO REQUEST INFORMATION ON PHARMACOLOGY OF HOE901 IN PREPARATION OF FDA MEETING 8/8/96.
96/08/08	49,078:960808	MMD Mtg	ALL		SUMMARY OF HOE901 MTG WITH FDA/ SUMMARY OF FDA MEETING ON AUG 8, 1996 TO DISCUSS THE CLINICAL DEVELOPMENT OF HOE901
96/08/09	49,078:960809	MMD Tel	Clinical		CONTACTS WITH JRHEE ON HOE901/ SUMMARIZES CONTACTS OF AUGUST 5 & 7 WITH J. RHEE, CSO FOR HOE 901

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96/09/09	49,078:960909	MMD Sub	Clinical	013	SUBMIT MTG MINUTES FOR 8-8-96/ SUBMIT HOE 901 MEETING MINUTES OF 8/8/96 MEETING. ALSO REQUESTED THE AGENCY'S MINUTES THAT DOCUMENT THIS INTERACTION AND REQUEST OPPORTUNITY TO RESPOND ON ANY POINTS, SHOULD HMR'S UNDERSTANDING DIFFER OR REQUIRE FURTHER CLARIFICATION.
96/09/20	49,078:960920	MMD Ltr	Pre-Clin	014	SUBMIT 6-MO DOG TOX STUDY/ PER SUGGESTION OF DR. JORDAN AT PRE-IND MEETING ON 10-25-95, SUBMIT 6 MONTH DOG TOXICITY STUDY CONDUCTED WITH HOE-901. NO UNEXPECTED FINDINGS.
96/10/07	49,078:961007	MMD Tel	Clinical		FOLLOWUP OF FDA MTG 8/8/96/ FOLLOW-UP WITH THE DIVISION ON SEVERAL ITEMS BROUGHT UP AT THE FDA MEETING ON AUGUST 8, 1996.
96/10/22	49,078:961022	FDA Tel	Clinical Pre-Clin		FU DOG STUDY,PHASE III,PREG WO/ FOLLOWUP ON WHETHER 12-MONTH DOG STUDY COULD BE WAIVED FOR HOE 901 AND INQUIRY IF AGENCY HAS DECIDED ON THE SIZE OF SPECIFIC SUBGROUPS FOR PHASE III TRIALS AND INCLUSION OF PREGNANT WOMEN IN THOSE TRIALS.
96/11/08	49,078:961108	MMD Sub	Pre-Clin	015	INFORMATION AMENDMENT/ SUBMIT A COPY OF COMPLETE REPORT RESULTS FOR 6-MONTH DOG TOXICITY STUDY CONDUCTED WITH HOE 901. VOLUME 1 OF 1

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96/11/18	49,078:961118	MMD Tel	Pre-Clin		EMBRYOTOX STUDY FOLLOWUP/ FDA REVIEWER LOOKING FOR RESPONSE TO FDA QUESTIONS ON EMBRYOTOXICITY STUDY OF 4/15/96 AND CONFIRMATION THAT FDA HAD RECEIVED 6-MONTH DOG TOXICITY STUDY SUBMITTED 11/8/96.
	49,078:961118A	MMD Tel	Pre-Clin		CONFIRM RECEIPT DOG ST REPORT/ CONFIRMATION OF RECEIPT/DISTRIBUTION TO FDA OF DOG STUDY REPORT SUBMITTED JULY 16, 1996. REQUEST FOR DECISION ON THE WHETHER A ONE YEAR STUDY WOULD BE REQUIRED IN DOGS. CONFIRM ATION OF NOV. 15 FDA MEETING TO DISCUSS THIS ISSUE.
	49,078:961118B	MMD Fax	Pre-Clin		RESPONSE TO 4/15/96 REQUEST/ PROVIDE INFORMATION IN RESPONSE TO QUESTION OF 4/15/96 RE: EMBRYOTOXICITY STUDY IN RABBITS WITH HOE 901. THIS WAS INITIALLY SUBMITTED ON 7/16/96 (S-012).
96/12/06	49,078:961206	MMD Tel	Clinical Pre-Clin		REQUEST FOR INFO ON 11/15 MTG/ SUMMARY OF SEVERAL ATTEMPTS TO GAIN ADDITIONAL INFORMATION FROM JRHEE REGARDING THE INTERNAL FDA MEETING ON NOV. 15, 1996 ON HOE 901.
97/02/10	49,078:970210	MMD Sub	Annual	016	ANNUAL REPORT 11/10/95-12/9/96/ 1ST ANNUAL REPORT COVERING THE PERIOD 11/10/95-12/9/96. FUTURE REPORT PERIODS TO BE 12/10-12/9.
97/03/04	49,078:970304	MMD Tel	Clinical		END OF PHASE II SUBMISSION PLA/ NOTIFICATION OF PLANS TO SUBMIT AN END OF PHASE II BRIEFING DOCUMENT TO FDA AT END OF WEEK OF MARCH 10, 1997.
97/03/13	49,078:970313	MMD Sub	Clinical		END OF PHASE II BRIEFING DOC./

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97/03/13	49,078:970313	MMD Sub	Clinical CMC Pre-Clin	017	END OF PHASE II BRIEFING DOC./ SUBMIT TO FDA END OF PHASE II BRIEFING DOCUMENT, REQUESTING MEETING WITH THE FDA TO REVIEW PHASE II AND DISCUSS PHASE III DEVELOPMENT OF HOE 901. VOLUME 1 OF 1.
97/03/14	49,078:970314	MMD Fax	Clinical		FAX: LPATTON/JRHEE/ FAXED COPY OF 3/13/97 COVER LETTER TO SOLOMON SOBEL, MD, SUBMITTING END OF PHASE II MEETING DOCUMENT, SERIAL NO. 117
97/03/24	49,078:970324	MMD Tel	ALL		SUMMARY OF 4 CONTACTS/ SUMMARIZES PHONE CONTACTS WITH JRHEE ON MARCH 13, 20, 24 AND RMISBIN ON MAR 20
97/03/28	49,078:970328	MMD Tel	ALL		FU ON END OF PHASE II MTG DATE/ FU ON MEETING DATE FOR THE HOE 901 END OF PHASE II MEETING WITH THE FDA
	49,078:970328A	MMD Sub	Clinical	018	END OF PHASE II BRIEFING DOC./ PER FDA REQUEST, SENT THREE ADDITIONAL COPIES OF THE HOE 901 END OF PHASE II BRIEFING DOCUMENT, WHICH IS IN ADDITION TO THE TWELVE COPIES SENT 3/13/97.
97/04/07	49,078:970407	MMD Tel	ALL		CONFIRM EOPHASE II MEETING/ PHONE CALL TO CONFIRM THE DATE FOR THE END OF PHASE II MEETING FOR HOE 901 AND SPECIFICS REGARDING THE METABOLISM SUPPLEMENT THAT WE PLAN TO SUBMIT.

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97/04/09	49,078:970409	MMD Sub	Clinical	019	END OF PHASE II BRIEF DOC SUPP/ PER 3-13-97 END OF PHASE II BRIEFING DOC (S-017), SUBMIT SUPPLEMENTAL METABOLISM INFORMATION, UPDATING METABOLISM SECTION AND PROVIDING THREE REPORTS: DOC NO. 016271, DOC NO. 015763 AND DOC NO. 016281 PLUS DOC 016284-ADDENDUM NO. 1.
	49,078:970409A	FDA Fax	Other		FAX: 5-1-97 MTG CONFIRMATION/ RECEIVED CONFIRMATION FROM FDA FOR 5-1-97 MEETING (10:00-11:30AM AT PARKLAWN BUILDING 3RD FL C/R "Q". AGENDA: 1. REVIEW OF PHASE 1 & 2 RESULTS 2. DISCUSSION OF PHASE 3 DEVELOPMENT PLAN.
97/04/15	49,078:970415	FDA Tel	ALL		QUESTIONS ABOUT BRIEFING DOC/ DR. MISBIN CALLED WITH QUESTIONS REGARDING THE BRIEFING DOCUMENT THAT WAS SUBMITTED FOR THE END OF PHASE II MEETING WITH THE AGENCY.
97/04/21	49,078:970421	FDA Fax	Other		FAX: MTG NOTICE/TACTILE CODING/ RECEIVED VIA FAX MEETING NOTIFICATION FOR TACTILE CODING (BRAILLE LABELING) WHICH WILL EFFECT HOE901 AND HR1799. DATE/TIME: JUNE 3, 1997 (2:00/4:00PM) AT PARKLAWN BUILDING 3RD FLOOR C/R "G" 5600 FISHERS LANE, ROCKVILLE, MD
97/04/22	49,078:970422	MMD Fax	Clinical		FAX: INFO FOR UPCOMING MTG./ PROVIDED REQUESTED INFO ON THE FINAL DOSES OF HOE 901 AND NPH INSULIN ADMINISTERED IN PHASE II PROTOCOLS 2002, 2003, 2004 AND 2005, DISCUSSED IN THE END OF PHASE II BRIEFING DOCUMENT TO DR. MISBIN. ASKED JRHEE PROVIDE TO DR. MISBIN FOR MAY 1, 1997 MEETING.

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97/04/22	49,078:970422A	MMD Ltr	Clinical	020	PROVIDE INFO FOR UPCOMING MTG./ PROVIDED REQUESTED INFO ON THE FINAL DOSES OF HOE 901 AND NPH INSULIN ADMINISTERED IN PHASE II PROTOCOLS 2002, 2003, 2004 AND 2005, DISCUSSED IN THE END OF PHASE II BRIEFING DOCUMENT TO DR. MISBIN. ASKED JRHEE PROVIDE TO DR. MISBIN FOR MAY 1, 1997 MEETING. COPY OF DATA FROM 49,078:970422
97/04/23	49,078:970423	MMD Fax	Other		FAX: PROVIDE DRAFT SLIDE PRES./ PROVIDED VIA FAX "DRAFT" SLIDES FOR THE END OF PHASE II MEETING WITH AGENCY ON MAY 1, 1997, INDICATING SLIDES MAY UNDERGO ADDITIONAL MODIFICATIONS PRIOR TO MAY 1ST MEETING.
97/04/25	49,078:970425	FDA Tel	ALL		SUMMARY OF 4/21,22,23,25 CNT/ SUMMARY OF CONTACTS OF APRIL 21 WITH DR. MISBIN AND APRIL 22,23, 25 WITH JRHEE.
97/04/28	49,078:970428	FDA Tel	Pre-Clin		PRECLIN TOX PROGRAM QUESTIONS/ RETURN CALL TO HERMAN RHEE. HE HAD TWO SPECIFIC QUESTIONS HE WANTED ADDRESSED REGARDING THE PRECLINICAL TOXICOLOGY PROGRAM.
97/05/01	49,078:970501	FDA Fax	Other		FAX: MTG ATTENDEE LIST/ RECEIVED ATTENDEE'S LIST FOR THE MAY 1, 1997, MEETING AT THE FDA FOR HOE 901 MEETING MINUTES FOR 5/1/97/ REVIEW PHASE II RESULTS AND GAIN GUIDANCE FROM THE AGENCY ON PHASE III PLAN. IN ADDITION, THE PHASE I PROGRAM AND PRECLINICAL DEVELOPMENT PROGRAMS WERE REVIEWED WITH THE AGENCY.
	49,078:970501A	MMD Mtg	ALL Clinical Pre-Clin		
97/05/06	49,078:970506	MMD Sub	CMC	021	INFORMATION AMENDMENT CMC/ UPDATE OF THE CMC SECTION OF IND

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97/05/08	49,078:970508	MMD Tel	CMC		CMC AMENDMENT SUBMISSION/ PHONE CALL TO JRHEE TO INFORM HER THE CMC AMENDMENT FOR HOE901 IN SUPPORT OF THE PHASE III CLINICAL TRIALS WAS SUBMITTED ON MAY 6, 1997.
97/05/13	49,078:970513	MMD Ltr	Pre-Clin	022	RESPONSE TO 4/28/97 PHONE CALL/ PER FDA REQUEST OF 4/28, PROVIDE COMPLETE COPIES OF SIX REFERENCES PROVIDED BY TOXICOLOGIST FOR HOE901 FOR FDA REVIEW.
97/05/22	49,078:970522	FDA Tel	Pre-Clin		REQUEST TOX REF DESK COPY/ PHONE CALL TO REQUEST A DESK COPY OF THE TOXICOLOGY REFERENCES THAT WERE PROVIDED TO THE DIVISION ON MAY 13, 1997 FOR REVIEW.
	49,078:970522A	MMD Ltr	Pre-Clin		LTR: LPATTON/RMISBIN/ PER FDA REQUEST, SENT DESK COPY OF REFERENCES PROVIDED TO THE AGENCY ON MAY 13, 1997 (SERIAL NO. 022), REGARDING NEUROLOGICAL CHANGES RESULTING FROM HYPOGLYCEMIA.
97/06/16	49,078:970616	MMD Sub	Clinical	023	NEW PROTOCOL 3004 & AMEND 1&2/ SUBMIT NEW PROTOCOL HOE 901/3004 SUBMIT CHANGE IN PROTOCOL: AMENDMENT NO. 1 DATED 5/21/97 AMENDMENT NO. 2 DATED 5/22/97
97/06/18	49,078:970618	MMD Ltr	Clinical Pre-Clin	024	SUBMIT MEETING MINUTES 5/1/97/ PROVIDE INTERNAL MEETING MINUTES FOR 5/1/97 MEETING WITH FDA AND REQUEST THE AGENCY'S MINUTES.

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97/07/02	49,078:970702	MMD Sub	Clinical	025	NEW PROTOCOL 3006 & AMEND 1/ SUBMIT NEW PROTOCOL HOE901/3006 SUBMIT CHG IN PROTOCOL FOR HOE901/3006 AND SUBMIT CHG IN PROTOCOL FOR HOE901/3004
97/07/18	49,078:970718	FDA Fax	Clinical Pre-Clin		HR1799/HOE901 MTG MIN 6/3/97/ DRAFT TACTILE CODING MEETING MINUTES OF 6/3/97 MEETING FORWARDED BY JRHEE. THIS IS F.Y.I. INSULIN INFORMATION (NOT SPECIFIC TO HOE901). COPY OF DATA FROM 99-999:970718
97/07/22	49,078:970722	MMD Sub	Clinical	026	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 STUDY #'S 003 (BOHANNON); 015 (FISH); 019 (GARG); 027 (HERSHON); 032 (KLAFF); 041 (NEIFING & BERGSTROM); 043 (RASKIN & AVILES-SANTA); 045 (REEVES); 047 (ROSENSTOCK);050 (SHEEHAN); 052 (SOLER); 053 (SPINOWITZ); 056 (WAHL) 057 (WEINSTEIN); 058 (WEISS).
97/07/23	49,078:970723	MMD Sub	Clinical	027	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3006 (NEW INV/NEW SUBS) STUDY NUMBER HOE 901/30060098 NEW INV: LESLIE JOSEPH KLAFF
97/08/01	49,078:970801	MMD Sub	Clinical	028	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 STUDY NUMBERS 001 BELL, 014 FINK, 017 FRIEDMAN, 018 GANDA, 022 GOLDBERG/MENEGHINI, 023 GOLDSTEIN/NAJM, 025 GUTHRIE/CHILDS, 031 KLACHKO/GRIFFING, 034 LITTLEJOHN III/JONES JR., 044 RATNER, 046 ROBERTS.

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97/08/01	49,078:970801A	MMD Tel	ALL Pre-Clin		SUMMARY OF CONTACTS 8/1,4,15/ SUMMARY OF CONTACTS OF AUG 1, 4, 15
97/08/07	49,078:970807	MMD Sub	ADR	029	10-DAY ADR REPORT/ SUBMIT 10-DAY REPORT CONCERNING RESULTS OBSERVED IN NON-CLINICAL ANIMAL TOX STUDIES. ALSO INCLUDED A COPY OF AN INFORMATIONAL LETTER TO BE SENT TO INVESTIGATORS AS WELL AS REFERENCES 1-6.
97/08/20	49,078:970820	MMD Tel	ALL Clinical Pre-Clin		49,078 10-DAY ADV EVT SUBMISS/ PHONE CALL TO FIND OUT OF FDA HAD COMMENTS REGARDING 10-DAY ADVERSE EVENT SUBMISSION 8/8/97 REGARDING CARCINOGENICITY STUDIES IN MICE & RATS
97/08/21	49,078:970821	MMD Sub	Clinical	030	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 STUDY NUMBERS 002 (BLEVINS/CHILES), 008 (DAILEY, III), 009 (DANDONA), 017 NEW SUBS ONLY & NEW RESEARCH FACILITY, 024 (PEK); 029 (JOVANOVIC), 038 (MCGILL), 049(SCHWARTZ), 051(SIVITZ) PROTOCOL HOE 901/3006, STUDY NO. 104 (SUH/BERGSTROM)
97/08/28	49,078:970828	MMD Sub	Clinical	031	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 (NEW INV/NEW SUBS) STUDY NO. 004 (BUSE/LARGAY) PROTOCOL HOE 901/3006 (NEW INV/NEW SUBS) STUDY NO. 066 (BELL); 068 (BOHANNON/ILIYA); 093 (HERSHON); 095 (KAMRATH/WEINSTEIN); 107 (REEVES); 111 (ROBERTS); 116 (SCHWARTZ).

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97/09/05	49,078:970905	MMD Sub	Clinical	032	PROTOCOL AMEND (NEW PROTOCOL)/ SUBMIT NEW PROTOCOL HOE 901/1013 DATED 8/25/97 STUDY NO. HOE901/1013/0127 NEW INV: ROBERT R. HENRY, MD & NEW SUBS
97/09/12	49,078:970912	MMD Sub	ADR	033	10-DAY FOLLOW UP REPORT/ FOLLOW UP TO 8/7/97 10-DAY IND SAFETY REPORT (SERIAL #S-029). PER FDA REQUEST FORWARDING INFO REQUESTED IN PHONE CALL OF 8/20/97, INCLUDING TABULATED RESULTS ALSO, SENDING SUBMISSION QUALITY REFERENCES TO REPLACE FAXED COPIES SENT IN EARLIER SUBMISSION (8/7/97).
97/09/16	49,078:970916	MMD Sub	Clinical	034	PROT AMND: S033 CHG'D TO S034/ PROTOCOL HOE901/3004 (NEW INV/SUBS) STUDY NO(S): 004 IRB CHG; 012 ABRAIRA; 026 BLOCK/HEILEMAN; 030 RAO/KELLEY/ STRONG; 048 SCHNEIDER; 059 WHITEHOUSE/ KAHKONEN/KRUGER PROTOCOL HOE901/3006 (NEW INV/SUBS) STUDY NO(S); 074 DONDONA; 090 GUTHRIE/ CHILDS 117 SPINOWITZ; 120 TAYLON/WAHL.
97/09/24	49,078:970924	MMD Tel	CMC		FOLLOWUP 6/9/97 MTG/CMC FORMAT/ FOLLOWUP ON SEVERAL ISSUES FROM JUNE 9 MTG WITH FDA AND DISCUSSION ABOUT THE FORMAT OF THE CMC SECTION OF HR 1799 AND HOE 901 NDAS.

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97/09/30	49,078:970930	MMD Sub	Clinical	035	PROT AMEND: NEW PROTS & AMEND/ NEW PROTOCOL: HOE901/1011 NEW PROTOCOL: HOE901/3005 & AMEND. NO. 1 PROTOCOL HOE901/3004 (NEW INV/NEW SUBS) STUDY NO(S): 005, 016, 017 SITE WITHDRAWN, 036,042. PROTOCOL HOE901/3006 (NEW INV/NEW SUBS) 072, 078, 096, 105, 108, 109, 118
97/10/16	49,078:971016	MMD Sub	Clinical	036	PROTOCOL AMENDMENT/ PROTOCOL HOE901/3004 (NEW INV & NEW SUBS STUDY NO(S): 010 DILLS; 013 FEINGLOS; 028 HIRSCH & EVANS; 037 MAYFIELD, TAYLOR & SHAIKH; 043 NEW SUB PROTOCOL HOE901/3006 (NEW INV & NEW SUBS 081 FELICETTA; 097 KILO; 099 LEVIN; 101 MORRISON & MALONE.
97/10/29	49,078:971029	MMD Sub	Clinical	037	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 (NEW INV/NEW SUBS) STUDY NO(S): 006 CLARK; 011 EISENBUD; PROTOCOL HOE 901/3006 (NEW INV/NEW SUBS) STUDY NO(S): 076 DILLS; 077 EISENBUD; 088 PEK; 091 HAMILTON; 100 EARL; 112 SCHNEIDER.
97/11/07	49,078:971107	MMD Sub	Clinical	038	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3005 (NEW INV/NEW SUBS) STUDY NO(S): 128, 129, 130, 132, 136, 137, 139, 140, 141, 142, 146, 148, 151, 152, 154, 155, 157, 160, 164, 168, 169, 173
97/11/10	49,078:971110	MMD Sub	Clinical	039	CHANGE IN PROTOCOL: PROT 1013/ SUBMIT AMENDMENT 1, DATED 10/30/97 TO PROTOCOL HOE 901/1013

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97/11/13	49,078:971113	MMD Tel	Clinical		UPCOMING SUBMISSION QUESTIONS/ CALL TO FDA TO RELAY UPCOMING SUBMISSIONS INFORMATION AND TO ASK SEVERAL QUESTIONS.
97/11/14	49,078:971114	MMD Sub	Clinical	040	GEN CORRES:DEV PLAN/SUB TIMING/ SUBMIT PROPOSED CLINICAL DEVELOPMENT PLAN WITH SUGGESTED TIME LINE.
97/11/20	49,078:971120	MMD Sub	Clinical	041	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 (NEW SUBS) STUDY NO(S): 0001 & 0037 PROTOCOL HOE 901/3005 (NEW INV/NEW SUBS) STUDY NO(S): 0133, 0135, 0150, 0153, 0156, 0161, 0167, 0170, 0171, 0174 PROTOCOL HOE 901/3006 (NEW INV/NEW SUBS) STUDY NO(S): 0069, 0071, 0083, 0089, 0092, 0114.
97/12/03	49,078:971203	FDA Tel	Clinical Pre-Clin		FOLLOWUP ON GUIDANCE ISSUES/ SUMMARY OF CONTACTW ON DEC. 3,5,12 AND 15 ON STATUS OF GUIDANCE ON INSULIN COLOR CODING AND OPTIPEN DEVICE SUBMISSION
97/12/04	49,078:971204	FDA Tel	Pre-Clin		RESPONSE TO PRECLIN INFORMATIO/ SUMMARY OF PHONE CONTACT IN RESPONSE TO QUESTIONS TO CSO REGARDING THE PRECLINICAL INFORMATION SUBMITTED 8/7/97 AND 9/12/97.
97/12/09	49,078:971209	MMD Sub	Clinical Pre-Clin	042	INFORMATION AMEND/ SUBMIT UPDATED INVESTIGATOR'S BROCHURE AND REPORT FROM THE EXPERT PANEL, INCLUDING CVS OF PANEL MEMBERS.

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97/12/11	49,078:971211	MMD Sub	Clinical	043	PROT AMEND & AMEND #2/ PROTOCOL HOE 901/3004 NEW SUBS PROTOCOL HOE 901/3005 AMEND #2 DATED 10/31/97 STUDY NO(S): 0147 (ROSENSTOCK); 0148 NEW SUBS; 0163 (RATNER); PROTOCOL HOE 901/3006 STUDY NO(S): 0080; 0085; 0113; 0122 (NEW INV/NEW SUBS); 0090 NEW SUB ONLY
97/12/12	49,078:971212	MMD Sub	Clinical	044	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3006 (NEW INVS/NEW SUBS STUDY NO. HOE 901/3006/ST0070 NEW INV: SEE STUDY NO. HOE 901/3006/ST0106 NEW INV(S): MAGEE & RATNER
97/12/16	49,078:971216	FDA Tel	Pre-Clin		INFO ON CARCINOGENI STUDIES/ RETURNED CALL TO DR RHEE WHO REQUESTED ADDITIONAL INFORMATION ON THE CARCINOGENICITY STUDIES
97/12/19	49,078:971219	MMD Sub	Clinical	045	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3004 ST0028 (NEW SUB) PROTOCOL HOE 901/3005 (NEW INVS/NEW SUBS ST0180 (JOSSE) ST0186 (GERSTEIN) ST0187 (GOTTESMAN)
97/12/22	49,078:971222	MMD Sub	Clinical	046	PROTOCOL AMENDMENT/ PROTOCOL HOE 901/3005 (NEW INVS/NEW SUBS ST0176 (BELANGER); ST0183 (GODIN); ST0184 (TILDESLEY).

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97/12/23	49,078:971223	MMD Sub	Clinical	047	PROT AMEND: NEW INV/NEW SUBS/ PROTOCOL HOE 901/3005 STUDY NO. HOE 901/3005/ST0181 NEW INV: DR. CINDY JO RICHARDSON & NEW SUB
98/01/15	49,078:980115	MMD Sub	Clinical	048	PROT AMEND: NEW INV/NEW SUBS/ PROTOCOL HOE 901/3004: STUDY NO(S) 045 CHANGE OF ADDRESS; 050 NEW SUB PROTOCOL HOE 901/3005: STUDY NO(S) 138 HIRSCH & EVANS; 144 MALONE & SHAH; 145 MAYFIELD & TAYLOR; 162 OLANSKY PROTOCOL HOE 901/3006: STUDY NO(S) 084 GANDA; 099 NEW SUB; 110 RICHARDSON; 113 NEW SUB.
98/02/03	49,078:980203	FDA Fax	Clinical Pre-Clin		FDA PHARM REVIEW COMMENTS/ RECEIVED PHARMACOLOGY REVIEW COMMENTS ON HMR 12/9/97 SUBMISSION.
98/02/05	49,078:980205	MMD Sub	Clinical	049	PROT AMEND: NEW INV/NEW SUBS/ PROTOCOL HOE 901/3004 ST0026 NEW SITE PROTOCOL HOE 901/3005 (NEW INV/NEW SUBS) STUDY NO(S); 131 BUSE & LARGAY; 159 COHEN; 172 MASHARANI; 178 HOULDEN 179 HRAMIAK; 185 UR; 189 BROADSTONE; 190 SMITH; 191 STOKES; 197 MATHER PROTOCOL HOE 901/3006 ST0102 MAYFIELD & TAYLOR; ST0125 GOLDBERG & MENEGHINI.
98/02/10	49,078:980210	MMD Sub	Annual	050	ANN RPT (12/10/96 - 12/09/97)/ SUBMIT ANNUAL REPORT FOR THE PERIOD DECEMBER 10, 1996 THRU DECEMBER 9, 1997

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98/02/16	49,078:980216	MMD Sub	Clinical	051	PROT AMEND: 3004/3006/ PROTOCOL HOE 901/3004 SUBMIT LIST OF RESPONSIBILITIES PROTOCOL HOE 901/3006 SUBMIT LIST OF RESPONSIBILITIES CHANGE IN PROTOCOL, SUBMIT AMENDMENT NO. 2 DATED 1/12/98
98/02/17	49,078:980217	MMD Sub	Clinical	052	PROT AMEND: NEW INV/NEW SUBS/ PROTOCOL HOE901/3005 (NEW INV/NEW SUBS) STUDY NO. 0177 (HALLE) STUDY NO. 0182 (ROSS)
98/02/18	49,078:980218	FDA Tel	Clinical		CNT RPT TX DIABETES MELLITUS/ DR. MISBIN CALLED TO REQUEST THE PARTICI TION OF INDUSTRY AT THE ADVISORY PANEL T O DISCUSS THEPROPOSED GUIDANCE "EVALUATION OF NEW TREATMENTS FOR DIABETES MELLITUS."
98/02/19	49,078:980219	FDA Tel	Clinical		CNT RPT: SUMMARY OF CONTACTS/ SUMMARY OF CONTACTS WITH FDA ON FEBRUARY 19 AND 26.
	49,078:980219A	MMD Tel	Clinical		CNT RPT ADV PANEL DISCUSSION/ PHONE CALLS TO OBTAIN ADDITIONAL INFO RE: ADVISORY PANEL MEETING 3/12/98 WHERE AGENCY WILL DISCUSS THE DRAFT GUIDEANCE "EVALUATION OF NEW TREATMENTS FOR DIABETES MELLITUS."
98/02/23	49,078:980223	FDA Fax	Clinical		DRAFT GUIDANCE EVALUATION/ PRELIMINARY DRAFT FROM FDA OF GUIDANCE EVALUATION OF NEW TREATMENTS FOR DIABETES MELLITUS--ADDITIONS 2/13/98. COPY OF DATA FROM 999999:980223

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98/03/03	49,078:980303	MMD Sub	Clinical	053	PROT AMEND: NEW INV/NEW SUBS/ PROTOCOL HOE 901/3004/ST0026 INVESTIGATOR RETIRED (HEILEMAN) PROTOCOL HOE 901/3005/ST0194 KULBACK PROTOCOL HOE 901/3006 STUDY NO(S): 0198 (MOORADIAN); 0200 (KULBACK); 0203 (GREENWAY & SMITH); 0204 (DRUCKER); 0206 (BERGER); 0207 (ANDERSON).
98/03/05	49,078:980305	MMD Fax	Clinical		HMR COMMENTS FOR ADV. PANEL/ AS REQUESTED, FAXED COMMENTS THAT HMR PLANS TO PRESENT AT THE UPCOMING 3/12/98 ADVISORY PANEL MEETING RE: DIABETES GUIDANCE DOCUMENT. COPY OF DATA FROM 999999:980305
98/03/13	49,078:980313	MMD Sub	Clinical	054	PROT AMEND: CHG IN PROT/ PROTOCOL HOE 901/3004/ST0058 NEW SUB PROTOCOL HOE 901/3005 CHG IN PROT AMEND #1 TO BE UTILIZED BY ADDED SITES; ALSO STUDY NO 0195 BERGER AS NEW INV. PROTOCOL HOE 901/3006 CHG IN PROT AMEND #1 TO BE UTILIZED BY ADDED SITES; ALSO STUDY NO 0199 SMITH AND STUDY NO 0208 (DIPPE) AS NEW INVS.
98/04/09	49,078:980409	MMD Sub	Clinical	055	CHANGE IN PROT/NEW INV/NEW SUB/ PROTOCOL HOE 901/3004: ST0032 NEW SUBS, ST0036 CHANGE TO IRB ADDRESS; ST0058 NEW SUB PROTOCOL HOE 901/3005: ST0144 CHG TO IRB ADDRESS; DISCONTINUED INV (SHAH) PROTOCOL HOE 901/3006: CHG IN PROT-- AMEND #2 DATED 1/12/98; 075 DEFRONZO; 086 GERICH; 0212 TOPIEL & PETERSON.

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98/04/13	49,078:980413	MMD Sub	Clinical	056	PROT AMEND: NEW INV/SUB 3006/ PROTOCOL HOE 901/3006 STUDY NO. ST0123 (BRAUNSTEIN)
98/04/23	49,078:980423	MMD Tel	CMC		CNT RPT MTG REQUEST/ CALL TO ASK QUESTIONS ABOUT TACTILE CODING AND COLOR CODING OF INSULIN PRODUCTS AND REQUEST CMC MEETING THIS SUMMER TO DISCUSS INSULIN NDAS COPY OF DATA FROM 99-999:980423A
98/04/27	49,078:980427	MMD Tel	Clinical		CNT RPT SUMMARY OF CONTACTS/ SUMMARY OF CONTACTS WITH JRHEE BETWEEN APRIL 27 - MAY 1 REGARDING QUESTIONS ABOUT NDA SUBMISSION.
98/05/07	49,078:980507	MMD Tel	Clinical		CNT RPT PED STUDY EXCLUSIVITY/ REQUEST TO FIND OUT THE CURRENT PROCEDURE FOR REQUESTING THE 6-MONTHS EXCLUSIVITY REGARDING PEDIATRIC STUDIES FOR UNAPPROVED DRUGS.
98/05/11	49,078:980511	FDA Tel	CMC		CNT RPT COLOR & TACTILE CODING/ CALL WITH INFORMATION LEARNED AT AN INTERNAL FDA MEETING REGARDING COLOR CODING AND TACTILE CODING OF INSULIN PRODUCTS. COPY OF DATA FROM 55,343:980511
98/06/02	49,078:980602	MMD Sub	Pre-Clin	057	RESP TO PRECLIN QUES (20 VOLS)/ SUBMIT 20 VOLUME SUBMISSION IN RESPONSE TO PRECLINICAL QUESTIONS RAISED BY THE FDA WITH REARD TO LONG ACTING INSULIN HOE 901.

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98/06/05	49,078:980605	MMD Sub	Clinical	058	PROT AMEND: NEW SUBS/SITE CHG./ PROTOCOL HOE 901/3004: STUDY NO(S) 0001 SITE ADDRESS CHANGE; 0043, 0056, 0059 NEW SUBS. PROTOCOL HOE 901/3005: STUDY NO 0155 NEW SUB. PROTOCOL HOE 901/3006: STUDY NO 0105 NEW SUB
98/06/09	49,078:980609	MMD Tel	Clinical Pre-Clin		PRECLIN INFO AMENDMENT/ CALLED J RHEE, SHE RETURNED CALL ON 6/10 I CALLED TO ADVISE HMR SUBMITTED A PRECLIN INO AMENDMENT ADDRESSING ISSUES RAISED BY AGENCY AND TO FIND OUT IF THE THE PACKAGE HAD BEEN RECEIVED. JULIE INDICATED THE AGENCY RECEIVED 6/3/98.
98/06/23	49,078:980623	MMD Tel	CMC		CALLED FDA WITH GEN CMC QUES./ CALLED DR. BERLIN TO ASK A COUPLE OF QUESTIONS ABOUT LEVEL OF DETAIL THE FDA NEEDS AN NDA REGARDING HPLC PURIFICATION COLUMNS, AND ABOUT THE TYPE OF SUBMISSION NEEDED FOR COLUMN SIZE CHANGES. COPY OF DATA FROM 55,343:980623
98/07/15	49,078:980715	MMD Sub	Pre-Clin	059	CARCINOGENICITY RPT AMENDS/ SUBMIT AMENDMENTS FOR CARCINOGENICITY REPORTS (DOC 017444 & 017375). FULL REPORTS SUBMITTED JUNE 2, 1998 (S-057).

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98/07/20	49,078:980720	MMD Sub	Clinical	060	PROT AMEND: CHG/ADD SITE ADDR./ PROTOCOL HOE 901/3004 STUDY NO. ST0057 (NEW SUB) PROTOCOL HOE 901/3005 STUDY NO(S): 128, 168 (CHG SITE ADDR) 157 (DELETION OF SITE); 140 NEW SUB PROTOCOL HOE 901/3006 STUDY NO(S): 099 NEW SUB; 122 CHG TO SITE ADDRESS.
98/07/24	49,078:980724	MMD Fax	Clinical		PROVIDE COVER LETTER OF S-061/ PROVIDE TO JULIE RHEE A COPY OF THE COVER LETTER TO DR. SOBEL RELATIVE TO PROPOSAL FOR NDA CRFS AND NARRATIVES (SEE GEN CORRES, S-061, DATED 7/24/98)
	49,078:980724A	MMD Sub	Clinical	061	GEN CORRES: PROPOSAL CRFS/NAR./ SUBMIT PROPOSAL FOR NDA CRFS AND NARRATIVES (ONE VOLUME SUBMISSION)
98/07/30	49,078:980730	MMD Sub	Clinical	062	PROT AMEND: SITE ADDRESS CHG/ PROTOCOL HOE 901/3004 (STUDY # ST0002) PROTOCOL HOE 901/3006 (STUDY # ST0122) CHANGES TO SITE ADDRESS FOR EACH
98/08/05	49,078:980805	MMD Ltr	Clinical CMC	063	GEN CORRES:PRE-NDA MTG REQUEST/ REQUEST A PRE-NDA MEETING, IF POSSIBLE, FOR MID TO LATE SEPTEMBER. ADVISED CMC QUESTIONS WILL BE ADDRESSED WITH THE AGENCY SEPARATELY. PROVIDED LIST OF HOE 901 TEAM REPRESENTATIVE FROM HMR TENTATIVELY SCHEDULED TO ATTEND. ALSO PROVIDED LIST OF REPRESENTATIVES FROM FDA THAT HMR WOULD REQUEST ATTEND.
	49,078:980805A	MMD Fax	Clinical CMC		FAXED COPY OF LETTER (S-063)/ PROVIDED TO JULIE RHEE VIA FAX A COPY OF THE 8/5/98 LETTER (S-063) DIRECTED TO SSOBEL, REQUESTING A PRE-NDA MEETING.

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98/08/06	49,078:980806	MMD Tel	Clinical		FOLLOW-UP WITH FDA/ LAVONNE PATTON CALLED JULIE RHEE TO FOLLOW-UP ON SEVERAL ISSUES. WHEN ASKED IF JULIE HAS RECEIVED OUR REQUEST FOR A PRE-NDA MTG, SHE RESPONDED YES. JULIE A WRITTEN REQUEST FOR PEDIATRIC DATA. ALSO INDICATED FDA NEEDED THE PRE-NDA MTG PACKAGE 2-3 WEEKS BEFORE THE FDA INTERNAL MTG.
	49,078:980806A	MMD Tel	Clinical		QUES TO FDA RE: PED STUDY/ LAVONNE PATTON CALLED KHYATI ROBERTS TO FIND OUT HOW TO SUBMIT A REQUEST REGADING HMR PEDIATRIC STUDY FOR 901 IN ORDER TO PROMPT THE DIVISION TO ISSUE A WRITTEN REQUEST FOR PEDIATRIC DATA.
98/08/07	49,078:980807	MMD Tel	Clinical		CONFIRM MESSAGE FROM AGENCY/ LAVONNE PATTON CALLED JULIE RHEE TO CONFIRM THE VOICEMAIL MESSAGE OF 8/7/98. JRHEE INDICATED THE AGENCY WOULD ACCEPT OUR PROPOSAL FOR SUBMISSION OF DATABASE PRINTOUTS FROM EUROPEAN STUDIES IN PLACE OF ANNOTATED CASE REPORT FORMS FOR SUBJECTS OTHER THAN THOSE REQUIRED, IE DEATHS & DROPOUTS DUE TO ADVERSE EVENT.
98/08/10	49,078:980810	FDA Tel	Clinical Other		DATE OF PRE-NDA MTG; 10/8/98/ JULIE RHEE CALLED WITH POSSIBLE DATE FOR HOE 901 PRE-NDA MEETING.
98/08/14	49,078:980814	FDA Fax	Clinical		PRE-NDA MEETING CONFIRMATION/ RECEIVED FROM FDA CONFIRMATION OF 10/8/98 PRE-NDA MEETING, ALONG WITH FDA ATTENDEES AND REQUEST FOR 10 DESK COPIES OF BRIEFING PACKAGE BY 9/9/98.

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98/09/03	49,078:980903	MMD Sub	Clinical	064	PROT AMEND: SITE ADD/NEW SUB/ PROTOCOL HOE 901/3005 STUDY NO 0128 CHANGE TO SITE ADDRESS STUDY NO 0132 NEW SUBINVESTIGATOR
	49,078:980903A	MMD Sub	Pre-Clin	065	INFO AMEND: PHARM/TOX/ SUBMIT PHARMACOLOGY/TOXICOLOGY PRECLIN MUTAGENICITY REPORTS (FULL REPORTS) FOR DOCUMENT NUMBERS: 015407, 016450, 015725, 013566, 012798, 016525. ALSO ADVISED WILL BE REFERENCED IN PRE-NDA BRIEFING PACKAGE AND ONLY INCLUDE SUMMARIES AT THAT TIME.
98/09/08	49,078:980908	MMD Sub	Clinical	066	GEN CORRES: PRE-NDA MTG PKG./ SUBMIT PRE-NDA MEETING PACKAGE FOR UPCOMING PRE-NDA MTG BETWEEN AGENCY & SPONSOR SCHEDULED FOR 10/8/98. (VOLUME 1 OF 1)
98/09/09	49,078:980909	MMD Tel	Clinical		PRE-NDA BRIEFING DOCUMENT/ LPATTON CONTACTED JRHEE ON 9/9/98 TO CONFIRM SHE RECEIVED THE PRE-NDA BRIEFING DOCUMENT SENT ON 9/8/98. LEFT VOICEMAIL AND CONFIRMED ON 9/10/98 THAT THE DOCUMENT HAD BEEN RECEIVED. ALSO ADVISED THE DISKETTE CONTAINING OUR QUESTIONS WAS SENT ON 9/9/98.
98/09/17	49,078:980917	MMD Sub	Clinical	067	GEN CORRES: PEDIATRIC STUDY/ OFFICIAL REQUEST OF METAB & ENDO DRUG PRODUCTS TO PROVIDE WRITTEN REQUEST TO HMR TO PERFORM A PEDIATRIC STUDY WITH HOE 901. THE PEDIATRIC PROTOCOL IN CHILDREN AGED 6-15 YRS WAS SUBMITTED TO HOE 901 IND AS PART OF THE PRE-NDA MEETING PACKAGE ON 9/8/98 (S-066) AND WAS ALSO ENCLOSED FOR FDA CONVENIENCE.

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98/09/29	49,078:980929	MMD Tel	Clinical		INQUIRY RE: PRE-NDA MTG PKG./ LAVONNE PATTON CALLED JULIE RHEE TO FIND OUT IF THE AGENCY HAD ANY QUESTIONS REGARDING THE PRE-NDA MEETING PACKAGE SUBMITTED ON 9/8/98.
98/10/02	49,078:981002	MMD Fax	Clinical Pre-Clin		RESPONSE TO FDA REQUEST/ FAXED TO JULIE RHEE INFORMATION REQUESTED BY HRHEE AT THE AGENCY PRE-NDA REVIEW MEETING FOR HOE 901 AND WAS PREVIOUSLY SENT TO AGENCY ON 7/16/96 (SERIAL NO. 012) IN RESPONSE TO HIS INITIAL REQUEST FOR ADDITIONAL INFO RE: VENTRICULAR DILATATION OF THE BRAIN IN HIMALAYAN RABBITS.
98/10/05	49,078:981005	FDA Tel	Pre-Clin		FDA INQUIRY FROM HERMAN RHEE/ DR. HERMAN RHEE CALLED LAVONNE PATTON REQUESTING ADDITIONAL INFORMATION RE: HIS PREVIOUS QUESTIONS ON THE OBSERVA- TION OF DILATATION OF BRAIN VENTRICLES IN THE FETUSES OF HIMALAYAN RABBITS WHO HAD BEEN DOSED WITH HOE 901 DURING PREGNANCY.
98/10/07	49,078:981007	MMD Tel	Clinical Pre-Clin		SUMMARIZE 10/7 & 10/8 CONTACTS/ LAVONNE PATTON CALLED JULIE RHEE ON 10/7/98 TO FIND OUT IF ADDITIONAL QUES- TIONS HAD BEEN RAISED RE: THE PRE-NDA MEETING SCHEDULED FOR 10/8/98 AND TO REQUEST HMR BE ALLOWED TO PRESENT THREE SLIDES AT THE BEGINNING OF THE MEETING.
98/10/08	49,078:981008	MMD Mtg	Clinical Pre-Clin		SUMMARY PRE-NDA MTG; CM-R/ EXEC SUMMARY HOE 901 PRE-NDA MEETING WITH AGENCY. NO SURPRISES OR NEW ISSUES. SUBMISSION ON TRACK FOR MARCH 1999.

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98/10/08	49,078:981008A	MMD Mtg	Clinical Pre-Clin		HMR PRE-NDA MTG MIN (10/08/98)/ SUMMARY OF PRE-NDA MEETING MINUTES FOR MEETING HELD ON OCTOBER 8, 1998, PROVIDING EXPANDED MEETING MINUTES. ALSO SEE 49,078:981008 FOR PREVIOUSLY DISTRIBUTED EXECUTIVE SUMMARY.
98/10/13	49,078:981013	FDA Tel	Clinical		SUMMARY 10/13 & 10/16 CONTACTS/ JULIE RHEE CALLED LAVONNE PATTON ON 10/13/98 AND REQUESTED THAT LAVONNE FAX HER COPIES OF THE THREE SLIDES PRESENTED AT THE PRE-NDA MEETING ON 10/8/98 AND FOLLOW UP WITH A HARD COPY OF THE SLIDES. THE SLIDES WERE FAXED TO JULIE ON 10/14/98.
98/10/16	49,078:981016	MMD Fax	Other		PROVIDE 3 OVERHEADS TO FDA/ PROVIDE VIA FAX COPIES OF 3 OVERHEADS PRESENTED AT THE BEGINNING OF PRE-NDA MEETING ON 10/8/98. THIS WILL BE FOLLOWED BY HARD COPY.
98/10/19	49,078:981019	MMD Sub	Clinical		ADDENDUM TO SERIAL NO. 067/ PROVIDE FDA WITH A COPY OF AMENDMENT #1 WHICH WAS MISSING FROM INITIAL SUBMISSION DATED 9/17/98 (SERIAL S-167).
	49,078:981019A	MMD Sub	Other	068	HARD COPY OF SLIDES TO FDA/ PROVIDE FDA HARD COPY OF 3 SLIDES THAT WERE PRESENTED AT PRE-NDA MEETING ON 10/8/98. COPIES WERE ALSO PROVIDED VIA FAX ON 10/16/98.
98/10/20	49,078:981020	FDA Tel	Pre-Clin		FOLLOW-UP ON PRECLIN QUES./ JULIE RHEE CALLED LAVONNE PATTON TO FOLLOW-UP ON THE PRECLINICAL QUESTIONS RAISED AT THE PRE-NDA MEETING.

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98/10/21	49,078:981021	MMD Sub	Clinical	069	PROT AMEND: NEW INV/SUBS 3006/ PROTOCOL HOE 901/3006 STUDY NO(S): 066 NEW SUBS, SITE CHANGES; 070, 081 NEW SUBS; 083 (SIMMONS), REPLACED FONSECA; 099 NEW SUB; 120 & 199 NEW SUBS, CHANGE TO SITE ADDRESS; 212 CHANGE TO SITE ADDRESS.
98/10/26	49,078:981026	FDA Tel	CMC		FDA REVIEWER CMC COMMENTS/ DR. WILLIAM BERLIN CALLED SUSAN ZORDAN TO RELAY SEVERAL COMMENTS FROM HIM REVIEW OF THE CMC INFORMATION IN THE HOE21PPR IND COPY OF DATA FROM 55,343:981026
98/11/04	49,078:981104	FDA Ltr	Clinical		FDA MINUTES OF PRE-NDA 10/8/98/ LETTER RECEIVED BY LAVONNE PATTON FROM SSOBEL (FDA), STATING ATTACHING COPY OF MINUTES OF PRE-NDA 10/8/98 MTG. HOWEVER, THERE WERE NO ATTACHMENTS. LPATTON GIVEN COPY OF LETTER, WHO WILL IN TURN CONTACT FDA TO OBTAIN.
98/11/06	49,078:981106	MMD Sub	Clinical	070	GEN CORRES: SPONSOR MTG MIN/ PROVIDE FDA SPONSOR MEETING MINUTES OF PRE-NDA MEETING HELDL 10/8/98 AND REQUEST THE AGENCY'S MINUTES.
98/11/10	49,078:981110	MMD Sub	Pre-Clin	071	GEN CORRES: PRECLIN ARTICLE/ PROVIDE FDA FOR REVIEW A COPY OF A TRANSLATED COPY ALONG WITH ORIGINAL LANGUAGE VERSION OF 1962 JOURNAL ARTICLE BY SALVATORE SCAGLIONE.

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98/11/12	49,078:981112	MMD Sub	Clinical	072	PROT AMEND: NEW SUBS/ PROTOCOL HOE 901/2005 STUDY # 0141 NEW SUB (GUERRERO) PROTOCOL HOE 901/3006 STUDY # 0106 NEW SUB (GRAY)
98/11/13	49,078:981113	MMD Tel	Clinical Pre-Clin		SUMMARY CONTACTS 11/13 & 11/17/ LPATTON CALLED JRHEE ON 11/13/98 TO FOLLOW UP ON OUTSTANDING ITEMS FROM PRE-NDA MEETING AND TO ASK IF DR. HRHEE HAD RECEIVED THE PRECLINICAL INFO SUB-MITTED ON 11/10/98 FOR HIS REVIEW. DR. JRHEE RETURNED THE CALL ON 11/17/98.
98/11/16	49,078:981116	MMD Sub	CMC	073	CMC MTG REQ & BRIEFING DOC./ REQUEST A PRE-NDA CMC MEETING WITH AGENCY AND PROVIDE BRIEFING DOCUMENT. REQUESTED A MID-DECEMBER MEETING.
98/11/17	49,078:981117	FDA Fax	Clinical		FDA MTG MINUTES (10/8/98 MTG)/ LPATTON RECEIVED FAX FROM JRHEE FDA OF ATTACHMENTS MISSING FROM FDA LETTER DATED 11/04/98. HARD COPY TO FOLLOW.
98/11/24	49,078:981124	MMD Tel	CMC		DISCUSS HOE901 AND HR1799/ SUSAN ZORDAN CALLED WBERLIN TO DISCUSS THE HOE 901 REQUEST FOR A CMC PRE-NDA MEETING AND TO INFORM HIM OF HMR'S DECISION NOT TO FILE THE HR 1799 NDAS.
	49,078:981124A	FDA Ltr	Clinical		COPY OF DATA FROM 55,343:981124 HARD COPY OF 11/17/98 FAX/ RECEIPT OF HARD COPY (AS PROMISED) OF 11/17/98 FAX PROVIDING COPY OF MISSING ATTACHMENT OF FDA LTR DATED 11/04.

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98/11/30	49,078:981130	MMD Fax	Clinical		NDA SECTION 11 PROPOSAL/ PROPOSAL TO FDA FOR SUPPLYING SECTION 11 OF THE NDA AS PART OF SECTION 8, WITH A CROSS-REFERENCE FROM SECTION 11 TO THE DATA APPENDICES IN SECTION 8 FOR EACH STUDY, ASKING IF THIS IS ACCEPTABLE TO AGENCY (HARD COPY TO FOLLOW -- S-074).
	49,078:981130A	MMD Sub	Clinical	074	PROPOSAL FOR NDA SECTION 11/ PROPOSE TO FDA TO SUPPLY SECTION 11 OF THE NDA AS PART OF SECTION 8, WITH A CROSS-REFERENCE FROM SEC 11 TO THE DATA APPENDICES IN SECTION 8 FOR EACH STUDY.
98/12/07	49,078:981207	FDA Tel	CMC		PRE-NDA CMC TELECONFERENCE/ JULIE RHEE CALL SUSAN ZORDAN TO SCHEDULE THE PRE-NDA METING OR TELECONFERENCE WHICH WE REQUESTED. THIS CONTACT COVERS SEVERAL TELEPHONE CALLS REGARDING ARRANGEMENTS FOR THIS TELECONFERENCE.
98/12/08	49,078:981208	MMD Tel	CMC		PRE-NDA CMC TELECONFERENCE/ THIS CONTACT REPORT DESCRIBES SEVERAL TELEPHONE CALLS WITH DR. WILLIAM BERLIN IN PREPARATION FOR THE HOE 901 PRE-NDA CMC TELECONFERENCE ON DECEMBER 17TH.
	49,078:981208A	MMD Sub	CMC	075	PROVIDE DISKETTE TO FDA/ IN PREPARATION FOR PRE-NDA CMC TELECONF, PROVIDED ELECTRONIC COPY OF THE DISCUSSION ITEMS FROM THE BRIEFING DOC SUBMITTED ON 11/16/98 (S-073).
	49,078:981208B	MMD Tel	Clinical		PRE-NDA MTG & NDA SECTION 11/ LPATTON CALLED JRHEE TO FOLLOW UP ON OUTSTANDING ISSUES WITH THE DIVISION REMAINING FROM PRE-NDA MTG IN EARLY OCT AND TO FOLLOW UP ON OUR LETTER REGARDING SECTION 11 OF THE NDA FAXED TO JULIE ON 11/30/98.

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98/12/11	49,078:981211	MMD Fax	CMC		FAXED COPY OF STABILITY PROT/ PROVIDED FDA WITH FAXED COPY OF THE STABILITY PROTOCOL FOR THE PRIMARY REGISTRATION STABILITY STUDIES FOR HOE 901 DRUG PRODUCT. HARD COPY TO FOLLOW.
98/12/15	49,078:981215	MMD Sub	CMC	076	RESPONSE TO FDA REQUEST/ PER PHONE CONVERSATION WITH WBERLIN OF FDA IN PREPARATION FOR 12/17 TELECONF, PROVIDED REQUESTED COPY OF STABILITY PROTOCOL FOR HOE 901 DRUG PRODUCT.
98/12/17	49,078:981217	MMD Tel	CMC		PRE-NDA CMC TELECONF;CM-R/ FDA AGREED WITH MOST PROPOSALS; SUGGEST- ED ADDITIONAL TESTS; EXPRESSED WILLING- NESS TO CONSIDER DELETION E COLI PROTEIN TEST; BIOAASAY/BIOIDENTITY TEST REQRMTS,
98/12/23	49,078:981223	FDA Ltr	Clinical		REQUEST FROM FDA RE PED STUDY/ FORMAL WRITTEN REQUEST FROM FDA RE: PROPOSED PEDIATRIC STUDY REQUEST SUBMITTED 9/17/98.
99/01/12	49,078:990112	MMD Fax	Other		FF ATTENDEES FOR 12/17 TELECON/ PROVIDE LIST OF FRANKFURT ATTENDEES AT 12/17/98 HOE 901 TELECONFERENCE.
	49,078:990112A	FDA Tel	Other		CNTRPTS: SUMMARIZE 1/12 & 1/14/ JULIE RHEE CALLED SUSAN ZORDAN 1/12/99 TO CONFIRM THE NAMES AND TITLES OF THE PARTICIPANTS IN THE 12/17/98 CMC PRE-NDA TELECONFERENCE. JULIE CALLED BACK ON 1/14/99 TO ADVISE SHE WAS FAXING THE FDA VERSION OF THE MINUTES.

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99/01/14	49,078:990114	FDA Fax	Other		MINUTES 12/17/98 CMC TELECONF./ FDA PROVIDED VIA FAX MEMORANDUM OF TELE-CONFERENCE MINUTES FOR CMC TELE-CONFERENCE HELD ON 12/17/98.
	49,078:990114A	FDA Tel	Clinical		IMPURITY SPECS FOR HOE 901/ SUSAN ZORDAN CALL DR. WILLIAM BERLIN TO DISCUSS THE IMPURITY SPECIFICATIONS FOR HOE 901 DRUG PRODUCT WHICH FDA REQUESTED AT THE PRE-NDA CMC TELECONFERENCE ON 12/17/98.
	49,078:990114B	MMD Tel	Clinical Pre-Clin		SUMMARY CONT RPTS 1/12 & 1/14/ LPATTON CALLED JRHEE. THIS CONTACT REPORT SUMMARIZES DISCUSSION WITH JULIE ON 1/12/99 AND 1/14/99 AND ARE FOLLOW UP ON OUTSTANDING ISSUES (SEE CONT REPORT DATED 12/8/98).
99/01/19	49,078:990119	MMD Tel	CMC		REVIEW QUES. RE: FDA MINUTES/ SZORDAN CALLED WBERLIN TO DISCUSS SEVERAL QUESTIONS ABOUT THE FDA MINUTES FROM THE PRE-NDA CMC TELECONFERENCE OF 12/17/98.
99/01/27	49,078:990127	MMD Tel	Clinical		CNT RPT: PEDIATRIC STUDY/ LPATTON CALLED DR. MISBIN TO FOLLOW-UP RE: THE WRITTEN REQUEST RECEIVED FROM THE AGENCY ON THE PEDIATRIC STUDY WITH HOE 901.
99/01/29	49,078:990129	MMD Sub	ALL	077	HMR NAMING QUINTILES US AGENT/ LETTER AUTHORIZING QUINTILES AS US AGENT EFFECTIVE JANUARY 4, 1999, FOR HMR.
99/02/01	49,078:990201	MMD Sub	ALL	078	QUINTILES ACCEPTS AGENT RESP./ QUINTILES ACCEPTS RESPONSIBILITY AS US AGENT FOR HMR EFFECTIVE 1/4/99.

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99/02/04	49,078:990204	MMD Tel	Clinical		DISCUSS PEDIATRIC EXCLUSIVITY/ LAVONNE PATTON CALLED ENID GALLIERS AT DR. MISBIN'S ADVICE TO DISCUSS THE DIFFERENCE BETWEEN HMRS REQUEST FOR PEDIATRIC EXCLUSIVITY AND THE AGENCY'S WRITTEN REQUEST.
99/02/10	49,078:990210	MMD Sub	Annual	079	ANN RPT (12/10/97 - 12/09/98)/ SUBMIT ANNUAL REPORT FOR THE PERIOD DECEMBER 10, 1997 THRU DECEMBER 09, 1998
99/02/11	49,078:990211	MMD Tel	Clinical		PRE-NDA MTG FOLLOW-UP/ LAVONNE PATTON CALLED JULIE RHEE TO FOLLOW UP ON THE REMAINING OUTSTANDING ISSUES FROM THE PRE-NDA MEETING HELD WITH THE AGENCY ON 10/8/99.
99/02/23	49,078:990223	MMD Sub	Clinical	080	PROT AMEND: NEW INV/SUBS 3006/ PROTOCOL HOE 901/3005 STUDY NO. 0156 (SITE CLOSED DUE TO LACK OF PATIENT ENROLLMENT. PROTOCOL HOE 901/3006 STUDY NOS: 0076 NEW INV: MEREDITH WHO REPLACED DILLS; 086 NEW SUB; 0110 NEW SUB.
99/02/25	49,078:990225	MMD Tel	Labeling		QUES RE: ANNOTATED LABELING/ SUSAN ZORDAN CALLED JULIE RHEE TO ASK SEVERAL QUESTIONS ABOUT THE ANNOTATED LABELING FOR HOE 901.

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99/03/09	49,078:990309	MMD Tel	Clinical		LABELING FOR HOE 901 NDA SUBM./ LAVONNE PATTON CALLED JULIE RHEE TO FIND OUT HOW SHE WANTED THE LABELING PROVIDED IN THE HOE 901 NDA SUBMISSION. JULIE WAS OUT OF THE OFFICE UNTIL MARCH 10. A MESSAGE WAS LEFT ASKING THAT JULIE RHEE CALL LAVONNE PATTON UPON HER RETURN. LAVONNE PATTON SPOKE WITH JULIE RHEE ON MARCH 11
99/03/16	49,078:990316	MMD Tel	Clinical		NDA SUBM. ELECTRONIC DATASETS/ CRAIG WILSON & LAVONNE PATTON CALLED DR. SAHLROOT, THE STATISTICAL TEAM LEADER FOR THE DIVISION ASSIGNED TO HOE 901, TO RELAY TO HIM THE DATASETS THAT WOULD BE PROVIDED ELECTRONICALLY IN SUPPORT OF THE STATISTICAL DOCUMENTATION FOR HOE 901 NDA SUBMISSION
99/03/17	49,078:990317	FDA Tel	Clinical CMC		FDA INQUIRY/ DR. BERLIN CALLED SUSAN ZORDAN WITH A QUESTIONS ABOUT THE COMPARATOR/COMPANION DRUGS USED IN THE CLINICAL STUDIES FOR HOE 901
99/03/19	49,078:990319	MMD Sub	Clinical	081	GEN CORRES:CLIN PHARM DATASETS/ PROVIDE FDA DATASETS FOR A SPECIFIED GROUP OF CLIN PHARM STUDIES SUPPORTING HOE901 NDA.
	49,078:990319A	MMD Sub	Clinical	082	GEN CORRES: PEDIATRIC STUDIES/ PROPOSED CHANGES IN THE WRITTEN REQUEST (FROM FDA DATED 12/23/98-- ATTACHMENT 1) FOR PEDIATRIC STUDIES (SEE ALSO OUR ORIG RESPONSE DATED 9/17/98--ATTACHMENT 2).

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99/03/23	49,078:990323	FDA Tel	Clinical CMC		REQUEST TO USE HMR NMR SPECTRA/ REQUEST BY DR. BERLIN TO USE SEVERAL HMR NMR SPECTRA FROM IND 55,343 HMR 1799 (HOE 21 PPR 100 PUMP INSULIN) IN A PRESENTATION HE IS MAKING @ PDA COPY OF DATA FROM 55,343:990323
	49,078:990323A	MMD Tel	Clinical		REGARDING 2 LETTERS SENT 3/19/ LAVONNE PATTON CONTACTED JULIE RHEE REGARDING TWO LETTERS SUBMITTED TO HER ON FRIDAY, MARCH 19, 1999
99/03/25	49,078:990325	MMD Tel	ALL		REQUEST FOR USER FEE NUMBER/ PHONE CONTACT TO REQUEST USER FEE NUMBER FOR SUBMISSSION OF NDA. NUMBER 3691 WAS ASSIGNED. KML
	49,078:990325A	MMD Tel	CMC		WHERE TO SEND NDA FIELD COPY/ SUE ZORDAN CALLED MARY WOLESKE AT THE KC DISTRICT OFFICE TO CHECK WHERE WE SHOULD SEND THE FILED COPY OF THE HOE 901 NDA
	49,078:990325B	MMD Tel	CMC		NMR SPECTRA IN PDA PRESENTION/ SUE ZORDAN CALLED DR. BERLIN TO LET HIM KNOW HE COULD USE THE NMR SPECTRA FROM IND 55,343 IN HIS PRESENTATION AT THE PDA MEETING NEXT MONTH. COPY OF DATA FROM 55,343:990325
	49,078:990325C	MMD Tel	CMC		WHERE TO SEND NDA FIELD COPY/ SUSAN ZORDAN PHONED ROCHELLE KIMMEL TO CHECK WHERE WE SHOULD SEND THE FIELD COPY OF THE HOE 901 NDA
99/03/26	49,078:990326	MMD Tel	CMC		WHERE TO SEND NDA FIELD COPY/ SUE ZORDAN CALLED ALAN MEHL TO CHECK WHERE WE SHOULD SEND THE FIELD COPY OF THE HOE 901 NDA

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99/03/31	49,078:990331	MMD Tel	ALL		NDA SUBMISSION QUESTIONS/ SEVERAL QUESTIONS FOR JULIE RHEE REGARDING THE NDA SUBMISSION. LEFT HER A VOICEMAIL MESSAGE ON MARCH 29 & ASKED HER TO CALL. JULIE RHEE RETURNED THE CALL ON MARCH 30, HOWEVER, LAVONNE WAS UNAVAILABLE. LAVONNE REACHED JULIE ON MARCH 31
99/04/08	49,078:990408	FDA Tel	CMC		12/98 CMC PRE-NDA TELEC. MIN./ DR. BERLIN CALLED TO FOLLOW-UP ON QUESTIONS WE HAD ABOUT THE MINUTES FROM THE DECEMBER 1998 CMC PRE-NDA TELECONFERENCE.
99/04/12	49,078:990412	MMD Tel	Clinical		RELAY HOE901 NDA SUBMIS. DATE/ LAVONNE PATTON CONTACTED DR. MISBIN TO RELAY THE SUBMISSION DATE FOR THE HOE 901 NDA
	49,078:990412A	MMD Tel	Clinical		OUTSTANDING ITEMS FOR NDA/ LAVONNE PATTON CONTACTED JULIE RHEE TO FOLLOW-UP ON THE OUTSTANDING ITEMS FOR THE HOE 901 NDA
99/04/19	49,078:990419	MMD Tel	Clinical		CONFIRM SUBMISSION DATE OF NDA/ TO CONFIRM WITH JULIE RHEE THE SUBMISSION DATE OF THE HOE 901 NDA
99/04/20	49,078:990420	MMD Tel	CMC		CARTRIDGE ROTATION TEST REVIEW/ SUE ZORDAN CALLED DR. BERLIN TO ASK IF HE WOULD BE WILLING TO REVIEW THE PROPOSED PROTOCOL FOR THE CARTRIDGE ROTATION TESTS FOR HOE 901

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99/04/20	49,078:990420A	MMD Fax	CMC		PERMISSION TO USE NMR SPECTRA/ PROVIDED COPY VIA FAX TO WBERLIN OF IN-USE ROTATION TEST PROTOCOL FOR HOE901 CARTRIDGES. ASKED FOR HIS COMMENTS ON THE ACCEPTABILITY OF THE PROTOCOL BEFORE THIS TESTING BEGINS.
99/04/21	49,078:990421	FDA Tel	CMC		CARTRIDGE ROTATION TEST/ DR. BERLIN LEFT A VOICEMAIL THAT THE CARTRIDGE ROTATION TEST PROTOCOL WAS ACCEPTABLE
99/04/26	49,078:990426	MMD Tel	ALL		CONFIRM AGENCY REC'D NDA/ TO CONFIRM THE AGENCY RECEIVED THE NDA AND TO LET JULIE KNOW I WOULD BE SENDING ADDITIONAL INFORMATION TO HER THIS WEEK.
99/04/29	49,078:990429	MMD Tel	ALL		QUESTIONS ON NDA SUBMISSION/ LAVONNE PATTON CONTACTED JULIE RHEE TO ASK ABOUT A NUMBER OF ITEMS RELATED TO THE HOE 901 NDA SUBMISSION. JULIE WAS NOT AVAILABLE SO LAVONNE LEFT A VOICEMAIL MESSAGE ASKING HER TO RETURN THE CALL. SHE CALLED BACK LATER THAT DAY.
99/05/03	49,078:990503	FDA Tel	CMC		CMC SECTION OF NDA/SITE REG./ DR. BERLIN CALLED TO SAY THAT HE HAD RECEIVED THE CMC SECTION OF THE NDA TODAY AND TO CLARIFY SITE REGISTRATION NUMBERS IN THE HOE901 NDA
	49,078:990503A	FDA Tel	Clinical		SUMMARY OF MAY 3/4/5 CONTACTS/ SUMMARY OF MAY 3/4/5. JULIE RHEE CALLED ON MAY 3 TO REQUEST 2 ADDITIONAL COPIES OF VOL.2 OF NDA. LAVONNE CONTACTED JULIE ON MAY 4 WITH ADDITIONAL QUESTIONS ABOUT SUBMISSION OF PEDIATRIC STUDY REPORT.

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99/05/04	49,078:990504	MMD Tel	CMC		MARBURG SITE REGISTRATION #/ SUE ZORDAN CALLED DR. BERLIN TO PROVIDE ADDITIONAL INFORMATION ABOUT THE SITE REGISTRATION NUMBER FOR THE MARBURG SITE
99/05/12	49,078:990512	FDA Ltr	Clinical		FDA AMEND TO WRITTEN REQUEST/ FDA APPROVED PROPOSED CHANGE AS SET OUT IN 3/19/99 (S-082) AND AMENDED FDA'S 12/23/98 WRITTEN REQUEST AS FOLLOWS (ALL OTHER TERMS REMAIN THE SAME): AGE GROUPS IN WHICH STUDY PERFORMED: AGES 6 THROUGH 11 YEARS AGES 12 THROUGH 15 YEARS
99/05/13	49,078:990513	FDA Fax	Clinical		REVISED PED WRITTEN REQ. LTR/ RECEIVED FAX FROM FDA PROVIDING COPY OF LETTER DATED 5/12/99 FROM FDA (HARD COPY TO FOLLOW). SEE 3/19/99A REQUEST (S-082). FDA REVIEWED PROPOSED CHANGES AND ARE AMENDING THE WRITTEN REQUEST REGARDING THE AGE GROUPS ACCORDINGLY, HOWEVER, ALL OTHER TERMS STATED IN 12/23/98 FDA LETTER REMAIN THE SAME.
	49,078:990513A	MMD Sub	Clinical		PED STUDY RPTS/PED EXCLUSIVITY/ 23 VOLUME SUBMISSION. PROVIDE PED STUDY IN RESPONSE TO FDA 2/4/99 CONTACT AND 5/12/99 FDA LETTER (PED STUDY 3003) FOR REVIEW WITH THE ORIGINAL NDA DATED 4/9/99 AND SUBMITTED ON 4/22/99. COPY OF DATA FROM 21-081:990513A
	49,078:990513B	FDA Tel	CMC		RESP TO FDA-PROJECT'S STATUS/ RESPONSE TO DR. BERLIN ABOUT THE STATUS OF IND 55,343 (HR 1799/HOE 21 PPR 100 PUMP INSULIN) COPY OF DATA FROM 21-081:990513

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Submission Date	Log Number IND/NDA:Date	Origin/ Type	Classi- fication	Supp/ Serial#	Description/ Comments
99/05/20	49,078:990520	MMD Tel	Clinical		SAFETY UPDATE/PROPOS. LABELING/ DISCUSS SAFETY UPDATE & CHANGES TO THE PROPOSED LABELING FOR HOE 901 BASED ON PEDIATRIC STUDY REPORT & 12-MONTH SAFETY STUDY
99/06/14	49,078:990614	MMD Tel	CMC		STATUS STERILIZATION VAL CM-R/ PROVIDE UPDATE ON STATUS OF THE STERILI- ZATION VALIDATIONFOR THE INSULIN GLARGINE CARTRIDGE AND ASK QUESTIONS ABOUT USE OF OPTIPEN FOR CLIN STUDIES. COPY OF DATA FROM 21-081:990614A

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99/11/02	49,078:991102	MMD Tel	Clinical		OPTIPEN PRO DEVICES IND INFO/ CONTACTED JULIE RHEE TO FOLLOW-UP ON CDRH REQUEST TO PROVIDE ADDN'L INFO ON OPTIPEN PRO DEVICES TO FULFILL THE IND INFO IN LIEU OF AN IDE SUBMISSION.
99/11/03	49,078:991103	MMD Fax	Clinical		FAX OUTLINING 4002 PROPOSAL/ FAX OF MEMORANDUM OUTLINING PROPOSAL FOR SUBMISSION OF PHASE IIIB PROT 4002 AND RESPONSE TO ADDITIONAL INFORMATION REQUESTED BY CDRH.
99/11/18	49,078:991118	FDA Fax	Clinical		FAX FROM FDA: CLARIFICATION/ RECEIVED FAX FROM JRHEE PROVIDING SOME CLARIFICATION FROM FDA
	49,078:991118A	MMD Sub	Clinical CMC	083	CMC & PROT AMEND, NEW PROTOCOL/ SUBMIT CMC & PROTOCOL AMENDMENT AS WELL AS NEW PROTOCOL 4002 (HOE901/4002).
99/11/23	49,078:991123	MMD Tel	Clinical		RE: FAX FROM CDRH REVIEWER/ ASKED IF WE COULD USE INFO FROM FAX PROVIDED BY CDRH REVIEWER RECEIVED NOV. 18, 1999
	49,078:991123A	FDA Tel	Clinical		REQUEST COPY OF PROTOCOL 4002/ DR MISBIN REQUESTED A DESK COPY OF PROTOCOL 4002
99/11/29	49,078:991129	FDA Fax	Clinical CMC		CLIN REVIEW COMMENTS/ FAX FROM FDA (JRHEE) PROVIDING THE CLINICAL REVIEW COMMENTS ON 11/18/99 SUBMISSION (S-083: 49,078:991118A)
	49,078:991129A	MMD Tel	Clinical		OPTIPEN PRO-REVIEWERS COMMENTS/ CALLED JULIE RHEE TO DISCUSS COMMENTS MADE BY CDRH REVIEWER REGARDING USE OF OPTIPEN PRO DEVICE IN HOE 901 PHASE IIIB PROTOCOL 4002

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99/12/02	49,078:991202	MMD Sub	Clinical	084	RESPONSE TO FDA REQUEST/ PER FDA REQUEST RECEIVED 10/18/99 RE: PHASE IIIB PROTOCOL 4002, PROVIDED INFO: 1) DESCRIBE ANY DEVICE LIFE ISSUES OR DURABILITY ISSUES IDENTIFIED FOR OPTIPEN 2) DESCRIBE ANY ISSUES OR PROBLEMS THAT THE PATIENTS SHOULD ANTICIPATE.
	49,078:991202A	MMD Fax	Other		FAX RE: TELECONFERENCE REQUEST/ PROVIDE VIA FAX SUMMARY OF THE POINTS HMR WOULD LIKE TO ADDRESS WITH DR. MISBIN AND DR. MALOZOWSKI IN A TELECONFERENCE.
99/12/08	49,078:991208	MMD Fax	Clinical		FAX RESPONSE TO COMMENTS 4002/ PROVIDE TO FDA VIA FAX RESPONSE FROM HMR TO COMMENTS RAISED BY DR. MISBIN AND DR. MALOZOWSKI ON HOE 901 PROTOCOL 4002. HARD COPY VIA FEDEX ALSO BEING PROVIDED.
	49,078:991208A	MMD Sub	Clinical	085	RESPONSE TO FDA REVIEWER QUES./ PROVIDE TO FDA RESPONSE FROM HMR TO COMMENTS FROM DR. MISBIN AND DR. MALOZOWSKI ON HOE 901 PROTOCOL 4002 WHICH WAS RECIVED VIA FAX ON 11/18/99.

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12/16/1999	049,078:19991216	QKAN TEL	Clinical		REQUEST INFORMATION Summary of Dec. 14 & 16: 1) Dr. Moh Jee Ng received submission of tumor codes in October. 2) CDRH reviewer agreed we could use info from his e-mail note to respond to questions from IRBs on protocol 4002 and can also refer the IRBs to 21 CFR Part 56. 3) Not anticipating questions over Christmas break.
12/17/1999	049,078:19991217	QKAN TEL	Clinical		REQUEST INFORMATION Questions regarding Dr. Sobels status as Director of the Division of Metabolism and Endocrine Drug Products.
01/04/2000	049,078:20000104	FDA TEL	Clinical		OTHER Julie requested 5 & 10mL vials and proposed labeling. They want to compare with other vials currently available on US market.
01/06/2000	049,078:20000106	FDA TEL	Preclinical		REQUEST INFORMATION Dr Herman Rhee, Preclinical Reviewer for HOE 901, requested additional information on the historical controls in NMRI mice for hepatocellular adenomas.
01/06/2000	049,078:20000106-A	FDA TEL	Labeling		REQUEST INFORMATION Dr Misbin called to request a clean copy of the updated Lantus labeling without the strikeouts and additions highlighted. He asked that this information be faxed to him.
01/07/2000	049,078:20000107	FDA TEL	Clinical		REQUEST INFORMATION Dr. Misbin called to discuss statements in our label regarding Ultralente. Will fax supporting statements from the submission.
01/07/2000	049,078:20000107-A	FDA TEL	Labeling		REQUEST INFORMATION Julie Rhee requested I send her an Electronic copy (with password protection on the file) of the HOE 901 labeling that was provided to Dr. Misbin by fax.
01/10/2000	049,078:20000110	QKAN SUB	Clinical	S-086	PROTOCOL AMENDMENT

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					New investigators/subs: Protocol HOE901/4002 Study no(s): 224 Bell, 226 Bloomgarden, 229 Bohannon, 233 Cannon, 234 Chaykin, 236 Davidson, 240 Drexler, 241 Montgomery, 250 Graf, 259 Khairi, 260 Khan, 265 Levy, 267 Lorber, 272 McClanahan, 276 Mersey, 277 Miles, 279 Podlecki, 281 Reeves, 283 Reynolds, 284 Riddle, 285 Rikalo, 286 Roberts, 288 Rosenstock, 289 Ross, 291 Schwartz, 294 Taylon, 298 Trujillo, 300 Vinik, 301 Weinstein, 303 Hershon, and 304 Neifing.
01/11/2000	049,078:20000111	FDA TEL	CMC		REQUEST INFORMATION Dr Komanduri asked questions related to the CMC file: how synthesis goes from tons to kg quantities. More CMC questions coming 1/12.
01/11/2000	049,078:20000111-A	QKAN TEL	Clinical CMC		REQUEST INFORMATION I asked if she'd located 5 & 10ml vials we sent (not yet located). Asked her about the CMC questions Dr Komanduri said he would send.
01/12/2000	049,078:20000112	FDA TEL	Clinical CMC		REQUEST INFORMATION Julie Rhee asked how the vials had been packaged. They cannot be located at FDA. Asked if we could send replacement samples to her today.
01/18/2000	049,078:20000118	QKAN SUB	Clinical	S-087	PROTOCOL AMENDMENT New investigators/subs Protocol HOE901/4002 Study No(s): 239 Dwarakanathan, 242 Fajtova, 247 Fonseca, 249 Gerich, 251 Grunberger, 255, Juneja, 256 Kaye, 257 Kayne, 258 Kent, 262 Klaff, 263 Leahy, 273 McGill, 293 Stoller
01/27/2000	049,078:20000127	QKAN LTR	EntireApplication	S-088	GENERAL CORRESPONDENCE Company name change from HMR to Aventis Pharmaceuticals Inc.
02/02/2000	049,078:20000202	QKAN SUB	ADR	S-089	15-DAY ADR REPORT(S) Mfg rpt # 200010026HAG initial

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02/03/2000	049,078:20000203	QKAN SUB	Clinical	S-090	PROTOCOL AMENDMENT Protocol HOE901/4002 Study No(s): 227 Bode, 246 Libanati, 252 Guthrie, 270 Malchoff, 274 Mehta, 275 Meredith, 280 Ratner, 282 Rendell, 287 Rodriguez-Oquendo, 288 new sub, 297 Trippe, 302, Weinstock, 305 Schneider.
02/08/2000	049,078:20000208	QKAN SUB	Clinical	S-091	PROTOCOL AMENDMENT Protocol HOE 901/4002 Study No(s): 225 Bernene, 237 Davidson, 238 Davis, 244 Feinglos, 245 Fink, 261 Kitabchi.
02/10/2000	049,078:20000210	QKAN SUB	Annual	S-092	ANNUAL REPORT Submit annual report for the period December 10, 1998 through December 9, 1999.
02/16/2000	049,078:20000216	FDA TEL	Clinical		REQUEST INFORMATION Dr. Wu called and introduced himself as a new CMC reviewer for the HOE 90l file. He stated he had some questions and we discussed them.
02/17/2000	049,078:20000217	QKAN SUB	ADR	S-093	15-DAY ADR REPORT(S) Mfg rpt # 199910343HAG initial
02/18/2000	049,078:20000218	QKAN SUB	Clinical	S-094	PROTOCOL AMENDMENT Change in Progocol, submiting Amendment 1 dated 1/13/2000 to Protocol HOE901/4002.
02/24/2000	049,078:20000224	QKAN SUB	Clinical CMC	S-095	PROTOCOL AND CMC AMENDMENT New Protocol/Amendment 1 Protocol HOE901/4003/ST0001 Transfer of Regulatory Obligations CMC
02/29/2000	049,078:20000229	QKAN SUB	ADR	S-096	15-DAY ADR REPORT(S) Mfg rpt# 200010026HAG(Follow up #1)
03/03/2000	049,078:20000303	QKAN SUB	ADR	S-097	15-DAY ADR REPORT(S) Mfg rpt # 199910343HAG (FU #1)

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03/15/2000	049,078:20000315	QKAN SUB	Clinical	S-098	PROTOCOL AMENDMENT Protocol HOE 901/4002 (invs & subs) Study No(s): 288 Boden, 230 Boden, 232 Buse, 235 Dailey, 243 Falko & Cottrell, 248 Francis, 264 Beichter, 269 Madhun, 295 Teague, 299 Vaswani.
03/21/2000	049,078:20000321	QKAN SUB	ADR	S-099	15-DAY ADR REPORT(S) Mfg rpt # 200010026HAG (FU #2)
03/28/2000	049,078:20000328	QKAN SUB	ADR	S-100	15-DAY ADR REPORT(S) Mfr rpt # 200010026HAG (FU #3)
03/29/2000	049,078:20000329	QKAN SUB	Clinical	S-101	PROTOCOL AMENDMENT Protocol HOE 901/4002 Study No(s): 0246 new sub, 0254 Henry, 0268 Louard, 0271 Marks, 0306 Raskin Protocol HOE 901/4003, study 0001 new sub.
04/17/2000	049,078:20000417	QKAN SUB	Clinical	S-102	PROTOCOL AMENDMENT Change in Protocol: Protocol HOE901/4002. Submit Prot Amend 2 dated 4/05/2000.