SYNOPSIS

Name of Sponsor: Abbott	**Individual** **Study Table:**	**(For National** **Authority** **Use only)**

Name of Finished Product:
Duodopa®

Name of Active Ingredient:
Levodopa-Carbidopa

Study Title:

A Long-term Health Economics Study of Intraduodenal Levodopa (Duodopa®) in Routine Care for Subjects with Advanced Idiopathic Parkinson's Disease with Severe motor Fluctuations and Hyper-/dyskinesia

DAPHNE (Duodopa in Advanced Parkinson's: Health outcomes & Net Economic impact)

Study Center(s) and Investigator(s):

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Publication (Reference):

S.E. Pålhagen; N. Dizdar; T. Hauge; B. Holmberg; R. Jansson; J. Linder; M Wainwright; H. Widner; A. Johansson. Interim analysis of a long-term study of intraduodenal levodopa in advanced Parkinson disease. Submitted to Neurology

Jerker Westin, ark Dougherty, Dag Nyholm, Torgny Groth. A home environment test battery for status assessment patients with advanced Parkinson's disease. Computer methods and programs in biomedicine published in 2009

Study Period:
15 March 2006 (first subject first visit) to

26 April 2011 (last subject last visit)

Phase of Development: IV

Objectives:

Primary Objective:
The primary objective was to collect health economic data depicting the initial levels and natural progression over time of resource usage, Parkinson's disease (PD)-related costs, and health related quality of life (HRQoL), utilizing both the Unified Parkinson's Disease Rating Scale (UPDRS) and the Euro QoL – 5 Dimensions quality of life instrument (EQ-5D), for a cohort of advanced PD patients treated with Duodopa, of which about one-third were Duodopa-naïve prior to the start of the study.

Secondary Objective(s):

- to characterize the stage of Parkinson's disease according to the Hoehn and Yahr Scale
- to rate the subject's best "ON" period according to the Schwab and England Scale
- to recognize cognitive impairment and assess cognitive changes according to the Mini Mental Status Examination (MMSE)
- to measure changes in depressive illness and response to therapy according to the
-       Montgomery-Åsberg Depression Rating Scale (MADRS)
- to study health related quality of life by using:
  o the Parkinson's disease specific quality of life instrument PDQ-39
  o an electronic home diary (exclusively Sweden)

Safety Objective:
To study the safety of Duodopa by assessing laboratory data, physical examinations, electrocardiograms, vital signs as well as adverse events throughout the course of the study.

Methodology:
Overall resource consumption was collected at baseline and throughout the study. The UPDRS, the most widely used instrument for rating symptom severity in studies of PD, was used to measure the progression of the disease over time and together with the EQ-5D to generate quality of life data (QoL). Changes from baseline for previously Duodopa-naïve patients were compared to changes over time for subjects previously treated with Duodopa.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
The planned number of subjects was 75. A total of 77 subjects were included in the study. One subject from the Duodopa naïve population withdrew consent before start of treatment. A total of 76 subjects were treated with Duodopa: 36 Duodopa naïve subjects (DN), 22 non-naïve subjects treated with Duodopa for <2 years (DNN<2) and 18 subjects being treated with Duodopa for ≥ 2 years (DNN$\geq$2).

Twenty-one out of 36 subjects in the DN population (58.3%), 16 out of the 22 subjects in the DNN<2 population (72.7%) and 12 out of the 18 subjects in the DNN$\geq$2 population (66.7%) completed the study.

Diagnosis and Main Criteria for Inclusion:
Advanced idiopathic Parkinson's disease.
- Subjects previously treated with Duodopa: Subjects on permanent treatment with Duodopa for at least 12 weeks prior to the study.

or
- Duodopa treatment naïve subjects: The Investigator previously considered changing conventional Parkinson's disease treatment.. The criteria for treatment outlined in the Summary of Product Characteristics for Duodopa had to be fulfilled.

Test Product, Dose and Mode of Administration, Batch Number:
Commercially available Duodopa was used for the trial. Duodopa was initially infused through a temporary nasoduodenal tube using the portable CADD Legacy Duodopa pump (CE 0473) to determine whether the subject responds favorably to this method of treatment and to adjust the dose before treatment with a permanent tube is started.

The dose was adjusted to an optimal clinical response for the individual subject, which means maximizing the functional ON-time during the day by minimizing the number of OFF episodes and the time OFF (bradykinesia) and minimizing ON-time with disabling dyskinesia.

The total dose/day of Duodopa was composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses.

Duration of Treatment:

Total duration: 36 months
The interim CSR was written after 12 months of treatment (CSR dated 11-Feb-2011).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable

Criteria for Evaluation

Efficacy:

Health Economics Measurements
Overall PD-related resource consumption was collected at baseline (month -3), at month 0, and monthly thereafter until study completion for Duodopa-naïve patients. Overall PD-related resource consumption was collected at month 0 and monthly thereafter until study completion for Duodopa-experienced patients.
The consumption of health care resources was "costed" using appropriate national product- or service-specific unit costs taken from the relevant sources (including price lists and fee schedules).

The UPDRS was used to measure disease progression, while the EQ-5D was used to generate QoL utilities. Duodopa-naïve patients were assessed at baseline (month -3), at month 0, and thereafter quarterly for the first year and biannually from month 12 to month 36 and Duodopa-experienced patients, were assessed first at month 0 and thereafter quarterly for the first year and biannually from month 12 to month 36.

Safety:

- Adverse events
- The following, including changes from baseline were summarized:
  - o Vitals signs
  - o Laboratory variables
  - o Electrocardiogram variables

Statistical Methods:

In order to estimate the health economics costs as precisely as possible it was desirable to get information from as many subjects on Duodopa treatment as possible. It was estimated that 75 subjects, who were willing to and who were capable of performing the tests, were to be recruited. Out of these 75 subjects it was desirable that 25 were Duodopa-naïve.

The primary endpoints were defined as change from baseline (baseline defined as Month -3) to the visit at Month 12. In addition, statistical analyses were also performed for visits at Month 0, 3, 6 and 9. Statistical analyses of efficacy were performed using the exact Wilcoxon signed rank test, and all safety endpoints were analyzed by means of descriptive statistics.

For all assessments standard summary measures such as mean, standard deviation, median and range have been calculated. In addition, change from baseline is presented for all endpoints. In the tables for UPDRS, EQ-5D, PDQ-39 and the electronic diary the nominal p-values are presented. Thus, no adjustment for multiple comparisons was performed and the p-values should be interpreted with caution.

Summary – Conclusions

This clinical study is the first investigation with a combination of efficacy, tolerability, Health Care Resource Utilization (HCRU) and QoL assessments using standard reference rating scales, subject questionnaires and subject eDiary

Disposition of Subjects

A total of 77 subjects were included in the study and 76 subjects were treated with Duodopa and allocated to one of the following 3 subgroups: 36 Duodopa naïve subjects (DN), 22 non-naïve subjects treated with Duodopa for <2 years (DNN<2) and 18 subjects being treated with Duodopa for ≥ 2 years (DNN≥2). Twenty-one subjects in the DN group (58.3%), 16 subjects in the DNN<2 group (72.7%) and 12 subjects in the DNN≥2 group (66.7%) completed the 36-month follow up in the study.

The reasons for premature study termination in the DN group were adverse events (19.4%), lack of efficacy, (13.9%), withdrawal of consent (5.6%), protocol violation (2.8%). In the DNN<2 and DNN≥2 groups, reasons for premature study termination were adverse events (22.7% and 11.1%, respectively), withdrawal of consent (11% of the DNN≥2 group) and protocol violation (4.5% and 11.1%, respectively).

Baseline Characteristics

In the DN group the mean duration since PD symptoms occurred was 12.6 (4.6) years, since PD diagnosis was 10.7 (4.0) years, and the mean duration of LVD treatment was 10.5 (4.2) years. The mean age when PD symptoms first occurred was 52.0 (5.8) years, when PD was diagnosed was 53.9 (±5.1) years and when LVD treatment was started was 54.1 (5.1) years.

In the DNN<2 and the DNN≥2 groups the PD history was different. The mean duration since PD symptoms occurred was 15.6 (4.7) and 19.2 (6.5) years, respectively, since PD diagnosis was 14.1 (4.9) and 17.6 (7.0) years, respectively. The mean duration of LVD treatment was 14.1 (4.7) and 17.5 (6.7) years, respectively, and the mean duration on Duodopa treatment was 1.2 (0.7) and 3.5 (1.3) years, respectively. The mean age when PD symptoms occurred were 49.8 (6.3) and 47.4 (10.9) years, respectively, when PD was diagnosed was 51.3 (6.2) and 49.1 (10.9) years, respectively, and when LVD treatment had been started was 51.2 (6.2) and 49.1 (10.7) years, respectively.

The UPDRS score at M0 were similar in all 3 subject groups (DN, DNN<2 and DNN≥2) with a mean total scores of 43.1 (16.7), 46.2 (17.3) and 47.8 (16.4), respectively. The mean scores of the UPDRS subscale I, II, III and, IV were also similar in all 3 subject groups.

The mean EQ-5D scores at for societal preferences and individual preferences were similar at M0 in all 3 subject groups.

The modified Hoehn and Yahr staging in the DN group revealed at current stage, at best stage and at worst stage mean scores of 2.5 (0.7), 2.0 (0.9) and 3.6 (1.1), respectively. Scores in the DNN<2 and the DNN≥2 groups tended to be slightly higher. The Schwab and England Activities of Daily Living Scale revealed in the DN, DNN<2 and the DNN≥2 groups mean scores of 80.4 (13.2), 75.5 (14.4) and 74.4 (11.5) respectively. The Mini Mental Status Examination (MMSE) were similar in all 3 subject groups at M0 with mean total scores of 27.8 (2.4), 28.0 (2.2) and 28.2 (1.4) in the DN, DNN<2 and DNN≥2 groups, respectively. Assessments using the Montgomery-Åsberg Depression Rating Scale (MADRS) were similar in all 3 subject groups (DN, DNN<2 and DNN≥2) with a mean score of 9.0 (5.3), 7.8 (5.2) and 8.8 (5.8), respectively.

The mean (SD) of the Parkinson's Disease Questionnaire PDQ-39 summary index in the DN group was 27.1 (11.8), was slightly higher in the DNN<2 (30.3 (10.7)) and highest in the DNN≥2 36.6 (15.4).

Medical History

The majority of subjects reported at baseline one or more medical disorders, and proportions were similar in the DN, DNN<2 and DNN≥2 groups (92.6%, 100.0% and 94.4%, respectively).

The highest incidences (40% to 80%) were reported for "psychiatric disorders", "musculoskeletal or connective tissue disorders" and "gastrointestinal disorders", with a similar proportion in all 3 subject groups for "psychiatric disorders" and "gastrointestinal disorders" and a lower incidence for "musculoskeletal or connective tissue disorders" in the DNN≥2 group as compared to the DN and DNN<2 groups. High incidences (20 % to 40%) were reported for "surgical and medical procedures", "vascular disorders injury", "poisoning and procedural complications", "nervous system disorders", "metabolism and nutrition disorders" and "renal and urinary disorders". The incidences were similar in all 3 subject groups for "surgical and medical procedures", "vascular disorders injury", "poisoning and procedural complications", "nervous system disorders" while the incidences for "metabolism and nutrition disorders" and "renal and urinary disorders" were higher in the DNN≥2 group as compared to the DN and DNN<2 groups.

Previous and Concomitant Medication

The majority of subjects in the DN, DNN<2 and DNN≥2 groups reported intake of dopaminergic agents (85.2%, 90.9%, and 72.2%, respectively). The most prominent group of concomitant medication administered to subjects in all 3 subgroups were: Psychoactive drugs, drugs to treat pain, drugs to compensate nutritional disorders, antibacterial drugs, as well as drugs for gastrointestinal disorders, prophylaxis for thrombosis, urological disorders, rheumatic disease and drugs for dementia.

Primary Efficacy Endpoint

In the DN group the mean UPDRS total score at BL (M-3) was 52.1 (16.1), the mean UPDRS score was significantly reduced at M0 (43.1 (16.7)), and changes were significant up to M18, being most prominent at M9. In the DNN<2 group the mean UPDRS scores remained similar up to M36 (47.1 (14.3) while mean scores in the DNN≥2 group showed a trend for a slight increase as of M24 to M36 (54.0 (25.3)). The mean scores of the UPDRS subscales I, II, III and IV in the DN, DNN<2 and DNN≥2 groups were similar at M0.

In the DN group the mean scores of all UPDRS subscales were lower at M0 when compared to BL and remained lower up to M9 (subscale I), up to M24 (subscales II and III) and up to M36 (subscale IV) when compared to BL values. The maximal changes were observed at M9 in subscale I, II and III and at M12 in subscale IV. In the DNN<2 and DNN≥2 groups, mean scores of all UPDRS subscales showed a trend to increase slightly over time when compared to M0 values. This trend was evident at longer observational periods and more prominent in the DNN≥2 group.

The outcomes of the EQ-5D instrument were different for the two assessments "Descriptive System" and "VAS". The EQ-5 D descriptive systems mean scores in the DN, DNN<2 and DNN≥2 groups at M0 were similar 0.67 (0.27), 0.68 (0.27) and 0.62 (0.24), respectively. In the DN group only the change of mean score between BL (M-3) and M0 was significant and in the DNN<2 and DNN≥2 groups mean scores remained unchanged from M0 to M36 including endpoint visit.

The EQ-5D VAS mean score in the DN, DNN<2 and DNN≥2 groups at M0 were similar 0.68 (0.18), 0.65 (0.18) and 0.58 (0.23), respectively. In the DN group the mean score at BL (M-3) was 0.44 (0.20) and all subsequent scores as of M0 to M36 were significantly increased. In the DNN<2 and DNN≥2 groups the mean scores remained unchanged from M0 to M36.

Figure 1: Results of Efficacy Endpoints: UPDRS, EQ-5D and PDQ-39: Total Scores for all Subpopulations on the Left and Change to Baseline for the Duodopa Naïve population on the Right.
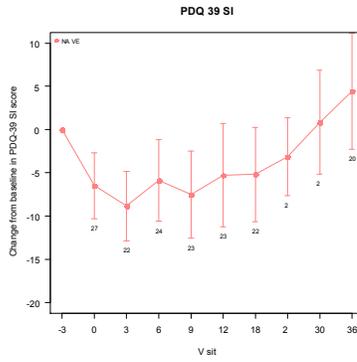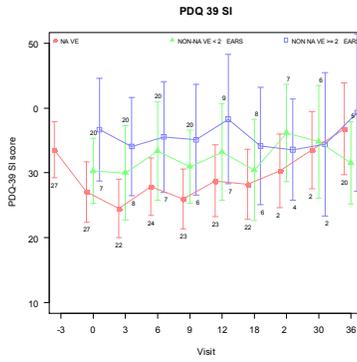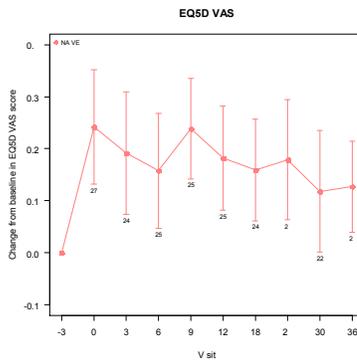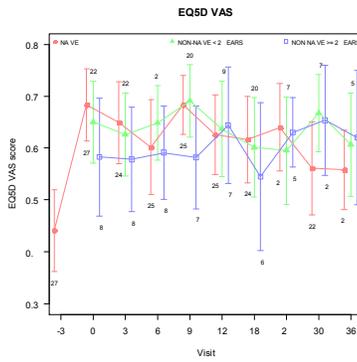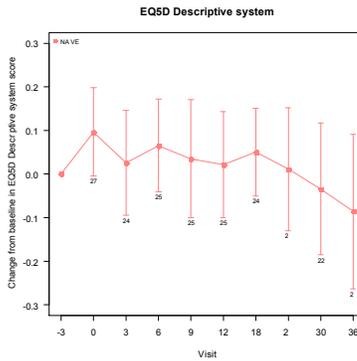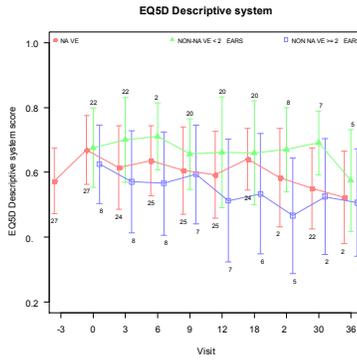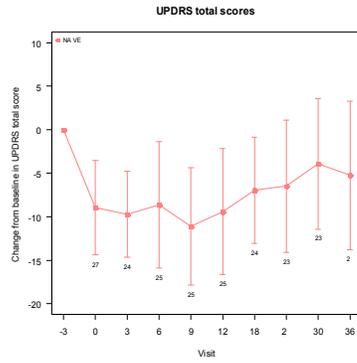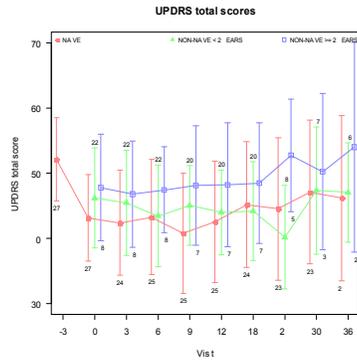
Table 1: Summary Overview on Statistics (Duodopa Naïve FAS): Change from BL to M12

	P-value	P-value imputed
UPDRS		
Total score	0.017	0.137
EQ-5D		
Descriptive system	0.919	0.601
VAS score	0.002	0.007
PDQ-39 SI		
Total score	0.126	0.714
Electronic Diary	Morning Scores	Day scores
1. Walking	0.016	0.188
2A. Off time (%)	0.008	0.107
2B. On time (%)	0.002	0.010
2C. Dyskinetic (%)	0.048	0.003
3. Off magnitude	0.001	0.003
4. Dyskinetic magnitude	1.000	0.002
5. Cramps	0.017	0.191
6. Satisfied with function	0.002	<0.001
7. Self assessment	0.047	0.847
8A. Free tapping - speed (taps/20 sec.)	0.012	0.035
8B. Free tapping - accuracy (%)	0.599	0.048
9. Tapping: increased speed – accuracy (%)	0.026	0.208
10A. Tapping: random chase - speed (taps/20 sec.)	0.010	0.073
10B. Tapping: random chase - Accuracy (%)	0.048	0.030
11. Drawing impairment (wavelet method)	0.208	0.048

Secondary Efficacy Endpoints

The mean scores of the modified H&Y Scale in the DN, DNN<2 and DNN≥2 groups at M0 were for the "current stage" 2.5 (0.7), 2.7 (0.8) and 3.2 (0.8), respectively, for the "best stage" (2.0 (0.9), 2.5 (0.7) and 2.5 (0.7), respectively and for the "worst stage" (3.6 (1.1), 3.7 (0.9) and 4.0 (0.6), respectively, and mean scores for all three stages were similar as of M0 to M36 and endpoint visit in all 3 subgroups.

The mean scores of the Schwab & England Scale at "best on" were similar 80.4 (13.2), 75.5 (14.4) and 74.4 (11.5), respectively, and mean scores in all 3 subgroups remained unchanged as of M0 to M36 and endpoint visit.

The means of the MMSE total score and the five subscale scores in the DN, DNN<2 and DNN≥2 groups were similar at M0 and no clinically meaningful changes were observed in any of the 3 subgroups up to M36 and endpoint visit.

The MADRS scores in the DN, DNN<2 and DNN≥2 groups at M0 were similar 9.0 (5.3), 7.8 (5.2) and 8.8 (5.8), respectively, and remained similar over time in all 3 subgroups.

Subject Questionnaires

The mean PDQ-39 total score at M0 was lowest in the DN group (27.1 (11.8)), intermediate in the DNN<2 (30.3 (10.7)) and highest in the DNN≥2 group (36.6 (15.4)).

In the DN group the reduction of the mean total PDQ-39 scores as compared to BL(M-3) was significant at M0 to M9 and at M18, being most prominent at M3, however, the mean total PDQ-39 at M36 and endpoint visit was considerable higher as compared to M0. Some of the mean subscales scores (e.g. mobility, activities of daily living, emotional well-being,

social support, cognitions and communication) showed also a trend for an increase over time and were higher at M36 as compared to M0.

In the DN group the reduction of the mean (SD) total PDQ-39 scores as compared to BL (M-3) was significant at M0 to M9 and at M18, being most prominent at M3. The mean (SD) total PDQ-39 at M36 was considerable higher as compared to M0. The mean scores of the following the subscales were lower at M0 when compared to BL: "mobility", "activities of daily living", "emotional well-being", "stigma", "cognitions" and "communication" and remained subsequently decreased up to M6 (cognitions), M9 (communication), M12 (emotional well-being) M18 (mobility and activities of daily living) and M30 (stigma). For the subscale "bodily discomfort" no changes in mean (SD) scores were observed in the DN group, whereas in the DNN<2 and DNN≥2 groups a trend for a slight decrease was observed over time. For the subscale "social support" the mean (SD) scores in the DN group started to increase as of M0 gradually over time. This trend was also evident in the DNN<2 and DNN≥2 group over time.

In the DNN<2 and DNN≥2 groups similar mean PDQ-39 total scores were observed as of M0 to M36 and endpoint visit. A trend for slight increases of the mean subscale scores was observed over time for 7 out of the 8 subscales: "Mobility", "activities of daily living", "emotional well-being", "stigma", "social support", "cognitions" and "communication" whereas in "bodily discomfort" a trend for a slight decrease was observed over time.

Electronic Diary

The eDiary consisted of 15 items assessing motor performance, complication of therapy, self-assessment, and various types of tapping at "Morning" and "Day" recordings.

In the DN group statistics of the electronic diary data revealed that the morning scores of the following 12 items were significantly changed at M12 compared to BL (M-3): "Walking", "Off time", "On time", "dyskinetic time", "Off magnitude", "cramp", "satisfied with function", "self-assessment", "tapping: increased speed – accuracy", "tapping: random chase – speed" and "tapping: random chase – accuracy", and that the day scores of the following 9 items were significantly changed: "On time, "dyskinetic time", "Off magnitude", "dyskinetic magnitude", "satisfied with function", "free tapping – speed", "free tapping – accuracy", "tapping: random chase – Accuracy" and "drawing impairment".

In the DNN<2 and DNN≥2 groups descriptive analysis similar mean scores in each of the 15 items were observed as of M0 to M36 and endpoint visit.

Extent of Exposure

The administered mean total daily dose were recorded and analyzed by volume of gel (mL) and converted to [mg]. In the DN, DNN<2 and DNN≥2 at the dose at M0 were 82.7 (27.4) mL [1654 mg], 68.3 (24.4) mL [1366 mg] and 75.7 (44.3) mL [1514 mg], respectively. During the treatment duration of 36 months the mean total daily dose increased slightly in the DN group to 92.4 (36.7) mL [1848 mg] at M36 while the mean total daily dose in the DNN<2 and DNN≥2 groups remained unchanged up to M36 (74.7 (25.6) mL [1494 mg] and 78.6 (29.8) mL [1572 mg], respectively).

Safety

Overall, the adverse event profile as observed in study S187.4.001 corresponds well with the already known safety profile of Duodopa. The majority of adverse events seem to be associated with the medical devices and the procedures associated therewith. These encompass device dislocations and stoma site infections, and inflammations. The other adverse events that were observed and that were not associated with the medical devices are mostly well known reactions that have also been described for other oral levodopa-carbidopa combinations. These encompass psychiatric disorders like hallucinations, depression, anxiety, but also nervous system disorders like dyskinesias, on-off phenomena and other symptoms of the underlying disease. All are considered to be covered by the currently valid reference safety information. Of particular interest are changes in laboratory parameters that might be indicative for abnormalities in vitamin metabolism. The observations of increased levels of Vitamin B12, folic acid and of homocysteine warrant special attention. However, as the observed changes in laboratory parameters have not been paralleled by clinical abnormalities, their relevance is so far unclear. Nevertheless, a correction of the observed deficiencies is recommended. No new safety concerns were identified, the ongoing monitoring efforts for potential and identified risks will continue.

Conclusion:

Duodopa showed clear beneficial effects on disease symptoms, motor performance and complications of therapy in the Duodopa naïve group. In the Duodopa naïve group the UPDRS and PDQ-39 total scores were significantly reduced up to M18 as compared to baseline. The results of the eDiary recordings revealed a significant increase in the proportion of "On-time" per day and reduction on "Off-time" per day. In addition, activities of daily living in advanced Parkinson disease subject and quality of live showed some amelioration. In DNN<2 and DNN≥2 groups with a mean duration of Duodopa treatment of 1.2 and 3.5 years before inclusion in the study and an overall Duodopa treatment duration of more than 4 and 6 years to end of study participation, the benefits were evident in terms of stabilizing the burden on of PD symptoms and compensating the underlying disease progression occurring at this advanced stage of PD.

The overall tolerability was well and the adverse event profile as observed in this study corresponds well with the already known safety profile of Duodopa. The majority of adverse events seem to be associated with the medical devices and the procedures associated therewith. These encompass device dislocations, stoma site infections and inflammations.

The observed clinical benefits were consistent across the different assessment instruments used in this study, such as rating scales, subject questionnaires and eDiary and the majority of observed improvements were persistent over a period of up to18 months in the DN group. In the DNN<2 and DNN≥2 groups, the majority of the recorded motor and non-motor symptoms as well as the patient reported outcomes remained stable and/or showed only minor to moderate deteriorations over longer time periods, taking into account that this collective was already treated with Duodopa up to 5.9 years prior to inclusion in this 3-year follow up. This "stabilizing effect" may be considered as benefit, and balanced against the constant progression of disease symptoms in this collective of late stage PD patients.