NIS REPORT SYNOPSIS

Study Title:

CARIATIDE (Compliance of AROmatase Inhibitors AssessmenT In Daily practice through Educational approach)

A European observational study to evaluate the impact of educational material on the compliance and persistence rates to adjuvant aromatase inhibitor (AI) medication for postmenopausal women with hormone sensitive early breast cancer

Study Period:

First subject in: 06 May 2008 Last subject out: 27 May 2011

International Coordinators:

Prof Patrick NEVEN (Leuven, Belgium)

Prof Mina TANNER (Tampere, Finland)

Investigators:

Study Investigators (from 248 centres in 18 countries) were qualified breast cancer specialists within the hospital or private practice setting. Participating countries were mainly European countries but also Australia and some Latin American countries were involved: Australia (9 centres), Austria (8 centres), Belgium (32 centres), Chile (3 centres), Columbia (6 centres), Croatia (6 centres), Czech Republic (6 centres), Finland (2 centres), France (60 centres), Greece (23 centres), Italy (9 centres), Peru (6 centres), Romania (18 centres), Sweden (6 centres), Switzerland (5 centres), Turkey (24 centres), United Kingdom (18 centres), and Venezuela (7 centres).

Objectives:

Primary objective:

- To assess and compare the compliance rate at one year of treatment between the two observational arms: Standard Treatment and Standard Treatment plus Education arm, evaluated by the Subject.

Secondary objectives:

- To assess and compare the compliance rate at one year of treatment between the two observational arms evaluated by the Investigator.
- To assess and compare the persistence rate on adjuvant AI medication at one year and at two years between the two observational arms evaluated by the Investigator.
- To assess and compare the compliance rate at two years between the two observational arms evaluated by the Subject and the Investigator.
- To assess time to treatment discontinuation of adjuvant AI medication in the two observational arms evaluated by the Investigator.
- To identify reasons for treatment discontinuation on adjuvant AI medication in the two observational arms.
- To evaluate additional parameters which may have an influence on adjuvant AI treatment compliance and persistence in the two observational arms.

Study design :
International, multi-centre, randomised, parallel-group, observational study.

Target population:
- Postmenopausal women with hormone sensitive early breast cancer

- Documented decision of treatment with upfront adjuvant AI medication (either anastrozole or letrozole) according to current Summary of Product Characteristics (SmPC) or current treatment with AI medication (either anastrozole or letrozole) according to current SmPC, that has not exceed thirteen weeks of treatment.

Treatment arms and duration :
Subjects were randomised in two observational study arms as follows:
- **Standard Treatment arm**: Standard clinical routine follow-up for adjuvant AI medication for two years.
- Standard Treatment plus Education arm: Standard clinical routine follow-up for adjuvant AI medication for two years plus additional educational material that was provided regularly during the first year.

Therapeutic strategy:
Subjects were assigned to either standard care or standard care plus supplementary educational material. Providing subject supplementary educational material did not interfere with the investigator's therapeutic strategy. The assignment of the Subject to a particular therapeutic strategy was decided in advance, independently of possible participation in this study.

Number of subjects:
Number of subjects recruited: 2758
Number of valid subjects: 2567 valid for efficacy analyses

Study endpoints:
Primary outcome variable:
Compliance rate based on the Subject's assessment and defined as the percentage of subjects assessed as compliant to adjuvant AI medication based on the following information collected after one year in all subjects, whether persisting or not with adjuvant AI treatment.
The Subject was asked about her daily medication intake as follows: "You were prescribed to take your hormone medication each day. However, it could be possible that sometimes you didn't take your medication, therefore how many tablets could you say that you actually did take during the last year?"

0 – none	0%
1 – few	[0%; 20%]
2 – less than half	[20%; 40%]
3 – approximately half	[40%; 60%]
4 – more than half	[60%; 80%]
5 – almost all	[80%; 100%]
6 – all	100%

A Subject was compliant when she scored 5 or 6. Otherwise, the Subject was non-compliant for all other scoring between 0 and 4.

Secondary outcome variables:
Persistence rate at one year and 2 years defined as the percentage of subjects with a persistent use of adjuvant AI medication i.e. the percentage of subjects who answered "Yes" to the following question : "Are you still taking the upfront hormone medication you were prescribed before you entered this study?". In all other cases (e.g. premature discontinuation from the study or switch to another type of hormonal medication), the Subject was classified as being a *non-persistent* user.

A subject was classified as a persistent user of adjuvant AI medication when the data, documented in investigator's case report form (CRF) (independent of the evaluation of compliance) supported the persistent intake of adjuvant AI medication since last study visit.

Other variables:
Time to treatment discontinuation defined as number of days between the date of first and last intake of AI medication.

Reason for discontinuation of AI medication.

Subject and Investigator Reported Outcome variables
Validated questionnaires have been analysed after one and two years:

- Subject's present and recent mental well-being evaluated by GHQ-12 questionnaire.
- Subject's satisfaction with care during the last hospital visit evaluated by EORTC INPATSAT-32 questionnaire.
- EORTC INPATSAT-32 for investigators.
- Subject's personal view of the present and recent tolerability of hormonal medication evaluated by Fact-ES questionnaire.

Exploratory variables:

- Confounding factors on the compliance rate and persistence rate (demographics and other baseline characteristics as well as information regarding family situation, education and employment status, other medication, other diseases, postmenopausal status, early breast cancer history and therapies etc).
- OPTIMA-X tool to identify which subjects are likely/unlikely to respond to adherence programme.
- Intentional and non-intentional compliance questions.
- Presence of interruptions, number and mean duration of interruptions.
- Reason(s) for interruption.
- Information regarding adjuvant hormone medication.
- Adjuvant hormone medication availability.
- Feedback on educational material (at 1 year visit only).

Determination of sample size:
The individual subject randomisation was in a 1:1 ratio, with equal numbers of subjects being allocated to the Standard Treatment arm (Group A) and to the Standard Treatment plus Education arm (Group B).

A sample size of 1300 subjects per group was deemed necessary i.e. a total sample size of 2600 subjects in the whole study based on the following assumptions:

- Significance level (two-sided): $\alpha = 0.05$
- Power: $1-\beta = 0.80$
- Statistical test: Fisher's exact test (two-sided)
- Compliance rate in Group A: 70%
- Statistically relevant difference in compliance rate: at least 5%.

Methods of statistical analysis:
All variables were analysed by treatment arm using usual descriptive statistics.

For compliance and persistence rates, statistical comparisons of the two randomisation groups were performed using a Cochran-Mantel-Haenszel test (CMH test) controlling for the stratification factors (AI medication and time since starting AI medication) with a two-sided significance level ($\alpha = 0.05$).

The time to treatment discontinuation was analysed with the log-rank test to compare the randomisation arms. Additionally, Cox Proportional Hazards model including the stratification factors, AI medication, time since starting AI medication and randomisation arm was performed to estimate the hazard ratio and its confidence interval between the two randomisation arms.

The reasons for non-completion of the adjuvant AI medication were summarised by randomisation arm and overall. Chi-square test was used to examine possible differences between the two randomisation arms.

A logistic regression was used to identify the most important confounding factors.

Summary tables were given for each OPTIMA-X item and the summary score by randomisation arm and subject compliance (first and second year).

Descriptive results :

Subject disposition:

2758 subjects were included. The randomised population consisted of 2757 subjects: 1378 in the Standard Treatment Arm (Group A) and 1379 in the Standard Treatment arm plus Education Material (Group B).

There was no difference between randomisation arms regarding stratification factors:

- 45% of the randomised population started AI medication up to 6 weeks before randomisation, 24% 6 to 13 weeks before randomisation, and 31% after randomisation.
- 66.5% received anastrozole; 25.5% letrozole; and 8% another AI medication.

11 subjects actually did not receive adjuvant medication during the study.

356 subjects discontinued prematurely the study during the first year (153 due to AI medication discontinuation and 86 lost to follow-up) and 257 within the second year (76 due to AI medication discontinuation and 121 lost to follow-up).

The one-year ITT was composed of 2567 subjects (93% of the randomised population): 1290 in Group A and 1277 in Group B.

The second-year ITT was composed of 2242 subjects (81%): 1122 in Group A and 1120 in Group B.

Baseline characteristics:

No relevant differences between randomisation arms were shown for baseline characteristics including demographics and disease characteristics. The mean (SD) subjects' age was 63 ± 9 years. The mean (SD) time since primary diagnosis was 6 (5.4) months. Unifocal breast cancer was diagnosed in 71% of subjects. Neo-adjuvant chemotherapy had been given in 8% of subjects. All subjects underwent surgery (breast-preserving surgery in 59% and mastectomy in 41%); 14% of subjects received hormone replacement therapy before surgery with a median duration of 7 years; post-operative radiotherapy was performed or was planned in 81% of subjects; post-operative chemotherapy was given in 47% of subjects. In all, 60% of subjects reported other diseases than breast cancer (mainly cardiovascular in 37%). Other treatment for

Main results and conclusion:

Primary efficacy variable: first year compliance to AI medication:

In the interim analysis (primary analysis), the overall compliance rate was 81% in Group A and 82% in group B. There was no statistically significant difference between the two randomisation groups (p=0.4524). This was confirmed in the final analysis with overall compliance rate of 80% in Group A and 82% in group B (p=0.3994).

In sensitivity analyses, there was no statistically significant difference between Group A and Group B for compliance to initial AI (final analysis: 75% *versus* 78%, respectively, p=0.1879) and for compliance to hormonal therapy (final analysis: 77% *versus* 78%, respectively, p=0.4290).

First year compliance – Final analysis (ITT population)

	Group A (N=1290)	Group B (N= 1277)	P-value
Primary compliance to AI			
Yes	1038 (80%)	1044 (82%)	0.3994
No	252 (20%)	233 (18%)	
N	1290	1277	
Compliance to initial AI			
Yes	972 (75%)	990 (78%)	0.1879
No	318 (25%)	287 (22%)	
N	1290	1277	
Compliance to hormonal therapy			
Yes	963 (77%)	977 (78%)	0.4290
No	293 (23%)	276 (22%)	
N	1256	1253	

Secondary analyses:

Persistence rate to adjuvant therapy:

The persistence rate was 83% in Group A and 84% in Group B (p=0.3670) at the end of first year and 90% in Group A versus 88% in Group B (p=0.2425) at the end of the second year.

Compliance rate at the end of the second year

At the end of the second year:

- the compliance rate to adjuvant AI medication was 82% in both randomisation groups (p=0.9926),
- the compliance to initial AI was 81% in Group A *versus* 80% in Group B (p=0.5541)
- the compliance to hormonal therapy was 82% in Group A *versus* 80% in Group B (p=0.3255).

Investigator and Subject compliance score

Comparison of Subjects' and Investigators' compliance scores showed agreement in 65% of scores in Group A and in 66% in Group B for the first year, and 68% and 67% for the second year.

Time to treatment discontinuation

During the 2-year follow-up period, 116 (8%) of subjects in Group A and 121 (9%) in Group B discontinued the adjuvant AI medication. The most important reason was side effects, reported in 161 subjects (6%) regardless of the randomisation arm.

The time to treatment discontinuation was not significantly different between randomisation arms (p=0.710, Log-rank test).

Subject and Investigator Reported Outcome Questionnaires

In the randomised population, the change from baseline was similar between randomisation groups for the GHQ-12 scores, and for the EORTC/INPATSAT-32 investigator and subjects scores. Also, no difference was shown in the FACT-ES scores at the end of the first or second year.