Prospective, observational, cohort study of Lonquex® (Lipegfilgrastim), used in clinical practice for the prophylactic treatment of chemotherapy-induced neutropenia in adult patients with solid and haematological tumours receiving myelosuppressive chemotherapy

(Study protocol codes: TV44689-ONC-40101 in Austria, XM22-ONC-40080 in Belgium/Luxembourg, XM22-ONC-40094 in Czech Republic, XM22-ONC-40075 and XM22-ONC-40084 in Italy, XM22-ONC-40093 in Slovakia, XM22-ONC-40072 in Spain, XM22-ONC-40078 in Poland, and XM22-ONC-40081 in The Netherlands)

Clinical Study Report: Phase IV

Study initiation date:	21 January 2015
Study completion date:	07 December 2017
Data lock point:	05 April 2018
Date of report:	13 June 2018

Sponsor Signatory: Maja Gasparic
Associate Medical Affairs Director
Oncology EU
TEVA Pharmaceuticals Europe B.V.
Amsterdam, The Netherlands

The study was conducted in accordance with Good Clinical Practice (GCP), Good Pharmacovigilance Practices (GVP) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2012) as well as the ENCePP Code of Conduct (2014).
The study complies with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (European Commission, 2008) and the 2012 Guideline on Good Pharmacovigilance Practice (GVP): Module VI. The study complies with the nature of non-interventional (observational) studies referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004).This study has been performed in compliance with Good Clinical Practice including the archiving of essential documents.

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SYNOPSIS

Name of company: TEVA Pharmaceuticals Europe B.V., The Netherlands **Name of finished product:** Lonquex® **Name of active substance:** Lipegfilgrastim	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study :
Prospective, observational, cohort study of Lonquex® (Lipegfilgrastim), used in clinical practice for the prophylactic treatment of chemotherapy-induced neutropenia in adult patients with solid and haematological tumours receiving myelosuppressive chemotherapy

Principal investigators:
The patients were recruited and included in the studies analysed in this report by 142 investigators in 9 European countries (Austria, Belgium, Czech Republic, Italy, Luxembourg, Poland, Slovakia, Spain and The Netherlands).

Study centres:
A total of 114 centres in the 9 European countries participated in the studies included in this report.

Publication (reference):
Two interim posters and one abstract were published:

1) P. Pichler, N. Claes, P. Mazza, B. Zurawski, P. Potocki, E. Petru, M. Sediva, J. Katolicka, F. Lanza, C. Fontaine. Use of lipegfilgrastim in clinical practice for the prophylaxis of chemotherapy-induced neutropenia: interim results of pan-European non-interventional study: Poster presented at ESMO 2016; Copenhagen, Denmark; October 2016. Abstract P1459.
2) N. Cascavilla, T. Wrobel, E. Hatzimichael, E. Wojciechowska-Lampka, P. Mazza, K. Kargar, M. Lenzhofer. Use of Lipegfilgrastim in Clinical Practice for the Prophylaxis of Chemotherapy-Induced Neutropenia in Lymphoma Patients: Interim Results of a Pan-European Non-Interventional Study: Abstract at EHA 2017; Haematologica. 2017; 102(s2) : p755 and poster presented at 46th National SIE Congress, Rome, Italy, October 2017

Study period: Study initiation date: 21 January 2015 Study completion date: 07 December 2017 Data lock point: 05 April 2018	**Clinical phase:** IV

Objectives:
The primary objective of this Phase IV study was to describe the effect of the long-acting G-CSF therapy Lonquex® (Lipegfilgrastim) used in prophylaxis on CT, and specifically, on delay of CT use, CT dose omissions and reduction in CT dose in patients receiving cytotoxic CT for solid and haematological malignancies, according to routine clinical practice.
The secondary objectives were to document:

- Description of the population of cancer patients treated prophylactically by lipegfilgrastim in terms of their baseline characteristics: (1) tumour type and stage, (2) CT regimen and use (i.e., adjuvant or metastatic), (3) Multinational Association of Supportive Care in Cancer (MASCC) Index score, (4) demographics including gender, age, ethnicity and performance status (PS), (5) co-morbidities and (6) FN risk 10-20% with additional risk or >20%.
- Description of effect on QoL and pain as measured by Brief Pain Inventory (BPI) and EORTC QLQ-C30.

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Study design:

- Multicentre, prospective, observational cohort study of cancer patients receiving cytotoxic CT and Lonquex® in outpatient and inpatient setting.
- Lonquex® has been administered at discretion of the physician
- Patients have been followed for the cycles in which Lonquex® was administered as either primary or secondary prophylaxis of neutropenia during the chemotherapy regimen until 6 to 8 weeks after the last dose of lipegfilgrastim.
- The studies included in this report have been performed in Austria, Belgium, Czech Republic, Italy, Luxembourg, Poland, Slovakia, Spain and The Netherlands.
- Completion of a study screening including patients' demographics and baseline data such as date of birth, planned CT regimen, additional FN risk factors were captured.
- In addition whether they receive G-CSF in primary prophylaxy (PP) or secondary prophylaxy (SP) was documented.
- For each cycle, chemotherapy (CT) and biological therapy (BT) treatment data was captured. CT and BT were administered at the discretion of the physician.
- After the last dose of lipegfilgrastim a last data collection was to be done after 6 to 8 weeks.
- All data were captured in an eCRF
- Completion of informed patient consent and signed consent forms was mandatory prior to inclusion in the study

Number of subjects:
1,339 patients enrolled
1,313 patients included in the safety population
1,305 patients included in the efficacy population.

Diagnosis and criteria for inclusion/exclusion:
Inclusion criteria:

- Adult cancer patient ≥18years.
- Patient receiving Lonquex® for PP or SP of CIN.
- Signature of a written informed consent document.

Exclusion criteria:
Patients were excluded from participating in this study if they met any of the following criteria:

- Participation in another clinical trial that investigated study drug that was not yet marketed.
- Patients with chronic myeloid leukaemia and myelodysplastic syndromes.
- The patient was a pregnant or lactating woman.

Study drug, dose, mode of administration, lot no.:
Lipegfilgrastim to be administered in accordance with the Summary of Product Characteristics

Reference drug/Comparator, dose and mode of administration, lot no.:
Not applicable

Duration of treatment:
At the discretion of the investigator. The patient should be followed up to 6-8 weeks after the last dose.

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Criteria for evaluation:

The primary endpoints were:

- The mean number of days of delay of CT for each cycle
- The proportion of patients with CT doses reduced, omitted or delayed for each CT cycle

The secondary endpoints were:

- Omission of BT
- Dose reduction of BT
- The baseline characteristics of patients receiving Lonquex®
- The incidence of FN in the first cycle and the incidence of FN in subsequent cycles
- The incidence of neutropenia (total and according to grade) in different cycles
- The number of days in hospital in different cycles for any reason, for reason of FN, or for reason of CIN
- The number of days in intensive care unit in different cycles
- The use of anti-infectives and anti-mycotics based on the number of days of treatment in different cycles
- The incidence of treatment with intravenous antibiotics due to FN or connected infections
- The incidence of AEs
- The incidence of ADRs
- The incidence of SAEs and SADRs
- The number of blood transfusions
- The mortality
- The evolution of the quality of life, in terms of EORTC QLQ-C30 and Brief Pain Inventory (BPI) scores
- The analysis of study population:
  - The proportion of patients with absolute or overall FN risk >20% receiving Lonquex®
  - The proportion of patients with FN risk 10-20% receiving Lonquex®
  - The proportion of patients with FN risk < 20% receiving Lonquex®

Statistical methods:

Descriptive statistics were used to characterize the population at baseline:

- Continuous variables were characterised by the N, n with missing data, mean, standard deviation (SD), median, minimum and maximum.
- Discrete variables were characterised by the N, n for each category, n with missing data and corresponding percentages.

All endpoints were analysed using descriptive statistics.

No formal statistical hypotheses testing were conducted.

AEs, SAEs, ADRs and SADRs were coded with the Medical Dictionary for Regulatory Affairs (MedDRA; Version 20.0) and were summarized by System Organ Class (SOC) and Preferred Term (PT)

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Summary:

Efficacy conclusions

The most common dose modification in these studies was dose delay, followed by dose reduction. Numerically more chemotherapy dose reductions were reported when Lonquex was administered in secondary then when it was administered in primary prophylaxis. Chemotherapy dose reductions were reported in 14.4% of patients in primary prophylaxis and 20.7% of patients in secondary prophylaxis. For chemotherapy dose delays, the values were relatively similar in the two prophylaxis categories. Chemotherapy dose delays were recorded in 30.0% of patients when Lonquex was administered as primary prophylaxis, and 30.9% of patients when administered as secondary prophylaxis.

However in patients experiencing any kind of CT/BT dose modifications, this was less commonly associated with febrile neutropenia or severe neutropenia. A total of 40.3% of patients who received Lonquex in primary prophylaxis experienced any kind of CT/BT dose modification in at least one of the cycles. However, only 3.1% and 9.9% of these modifications were associated with febrile neutropenia or grade 3/4 neutropenia, respectively. In the group patients receiving Lonquex in secondary prophylaxis, 46.8% of them experienced some CT/BT dose modification throughout the study. However, only 9.1% and 19.3% of these modifications were associated with febrile neutropenia or grade 3/4 neutropenia, respectively.

In the cycle following the first Lonquex administration, CT dose delays were recorded in 13.2% of patients in PP and 11.0% of patients in SP. CT dose reductions were recorded in 8.1% of patients in PP and in 19.2% of patients in SP.

Although reported in a different way there is an alignment with interim data of another non-interventional study NADIR [11-13]. In NADIR study dose reductions were the most common dose modifications (22.4% of non-Hodgkin lymphomas, 17.0% of breast cancer patients and 5.8% of lung cancer patients receiving Lonquex either in PP or SP). However, CT dose modifications were rarely associated with chemotherapy-induced neutropenia (0.7% of all cycles in non-Hodgkin lymphomas, 0.7% of all cycles in breats cancer patients and 1.6% of all cycles in lung cancer patients) [11-13].

In the phase III RCT in breast cancer patients receiving lipegfilgrastim as primary prophylaxis chemotherapy dose delays in CT cycle 2 were observed in 16.2% patients, with no dose omissions or reductions [9]. However, the difference between data obtained in this study and the Bondarenko et al. [1] study can be explained by much more controlled setting of RCTs compared to real-world studies, more homogeneous population than in RCTs, as well as different study population in terms of tumor types (breast cancer vs different solid tumors and haematological malignancies).

Febrile neutropenia was observed in 3.1% of patients receiving lipegfilgrastim as PP and in 8.0% of patients receiving it as SP. There were more patients affected by grade 3/4 neutropenia in SP (21.3%) than in PP (13.4%).

The incidences of grade 3/4 neutropenia in this study are lower than the ones observed in the NADIR study (interim analysis), in which grade 3/4 neutropenia has been observed in 37.1% of non-Hodgkin lymphoma patients, 29.4% of breast cancer patients and 33.1% of lung cancer patients receiving lipegfilgrastim either as primary or secondary prophylaxis. The incidence of grade 3 febrile neutropenia in the same study was 2% in non-Hodgkin lymphoma patients, 2.2% in breast cancer patients and 0.6% in lung cancer patients [11-13].

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In RCT phase III study in breast cancer patients who were receiving lipegfilgrastim in primary prophylaxis no patient experienced febrile neutropenia in CT cycle 1. On the other hand sever neutropenia has been reported in 43.6% of patients in CT cycle 1, and in 50.0% of patients across all cycles [1].
The use of anti-infectives and anti-mycotics in this study was relatively high (30.5% and 10.0% of patients respectively). They were mainly used prophylactically.
Overall, lipegfilgrastim was effective in preventing incidence of febrile neutropenia and severe neutropenia in the real-world practice and the data were comparable with published data in similar population in similar study setting.

Safety conclusions:
A total of 21.6% of patients reported at least one ADR, whereas serious ADRs were reported by 3.2% of patients. The most frequent ADRs (>1%) in terms of % of affected patients were bone pain (5.86%), myalgia (3.43%), back pain (1.83%), arthralgia (1.68%) and pyrexia (1.14%). All the other ADRs had a frequency lower than 1%. As a consequence of ADRs or SADRs, the study was discontinued in 2.3% of patients.
Lipegfilgrastim is well tolerated in the real-world setting administered either in primary or secondary prophylaxis in patients with solid or haematological malignancies receiving cytotoxic CT.
Safety data obtained in this study are in line with published data for lipegfilgrastim and are expected for G-CSFs.

Conclusions:
In this non-interventional studies patients with solid or haematological malignancies treated with myelosupressive chemotherapy received Lonquex in primary or secondary prophylaxis, whereby majority of patients received it in primary prophylaxis (82.9%).
Among those receiving it a primary prophylaxis 82.4% of patients received Lonquex starting from chemotherapy cycle 1. In chemotherapy cycle 1, Lonquex was administered on time after the CT cycle (no delay; i.e. Lonquex was administered one day after the last administration of chemotherapeutic agent in the respective cycle) in 898 cycles (98.0%). The time delay went from 2 to 30 days in the 12 cycles (1.3%) where Lonquex was not administered on time after the CT cycle.
Lipegfilgrastim is effective and well tolerated in the real-world setting administered either in primary or secondary prophylaxis in patients with different tumor types receiving cytotoxic CT, both in terms of CT dose modifications and incidences of febrile neutropenia and grade 3/4 neutropenia.
Both effectiveness and safety data obtained in this study are in line with published data for lipegfilgrastim [1,9-13].

References:
Not applicable

Date of report:
13 June 2018

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LIST OF ABBREVIATIONS

ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ANC	absolute neutrophil count
BPI	brief pain inventory
BT	biological/targeted cancer treatment
CFR	Code of Federal Regulations
CI	confidence interval
CIN	chemotherapy-induced neutropenia
CRF	case report form
CRO	contract research organization
CT	Chemotherapy
DSN	duration of severe neutropenia
eCRF	electronic case report form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer
EOS	end of study
EU	European Union
FN	febrile neutropenia
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
i.v.	Intravenous
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLT	Lower Level Term
LSO	local safety officer
MASCC	Multinational Association of Supportive Care in Cancer
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small-cell lung cancer
PEG	polyethylene glycol
PhV	Pharmacovigilance
PP	primary prophylaxis
PS	performance status
PT	preferred term
QoL	quality of life
r-metHuG-CSF	recombinant N-methionyl form of human granulocyte colony-stimulating factor
s.c.	Subcutaneous
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure
SP	secondary prophylaxis
ULN	upper limit of the normal range

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, any amendments, the informed consent and other information that required pre-approval were reviewed and approved by IECs or IRBs, in the nine participating European countries. The IECs/IRBs of the nine countries are listed in the next sections by alphabetical order.

1.1.1. IECs in Austria

- Ethics Committee of Medical University Graz
- Ethics Committee KH Barmherzige Brüder –Standort Graz
- Ethichs Committee of Medical University Vienna
- Ethics Committee of City of Vienna
- Ethics Committee of Bundesland Salzburg
- Ethics Committee of Land Niederösterreich

1.1.2. IECs in Belgium/Luxembourg

Number	Participating sites	Address	Principal Investigator	EC
1	**UZ Brussel**	Laarbeeklaan 101 1090 Brussel Belgium	Dr Fontaine Christel	Commissie Medische Ethiek UZ Brussel
4	**AZ Maria Middelares**	Kortrijksesteenweg 1026 9000 Gent Belgium	Dr Elzo Kraemer Ximena	Ethisch Comité AZ Maria Middelares
5	**AZ Alma - Eeklo**	Moeie 18 9900 Eeklo Belgium	Dr Thienpont Muriël	Commissie voor Ethiek AZ Alma
6	**AZ Monica - UZA**	Florent Pauwelslei 1 2100 Deurne Belgium	Prof Peeters Marc	Ethisch Comité UZA
7	**AZ Sint-Jan Brugge - Oostende AV**	Ruddershove 10 8000 Brugge Belgium	Dr Claes Nele	Commissie voor Ethiek AZ Sint-Jan Brugge-Oostende AV
8	**AZ Damiaan**	Gouwelozestraat 100 8400 Oostende Belgium	Dr Spoormans Isabelle	Ethisch Comité AZ Damiaan
9	**AZ Sint-Rembert**	Sint-Rembertlaan 21 8820 Torhout, Belgium	Dr Mispelaere	Commissie Medische Ethiek AZ Delta

Number	Participating sites	Address	Principal Investigator	EC
11	**Clinique et Maternité Sainte Elisabeth**	Place Godin 15 5000 Namur Belgium	Dr Vuylsteke Peter	Comité d'Ethique Clinique et Maternité Sainte Elisabeth
12	**CHU Brugmann - Victor Horta**	Arthur Van Gehuchtenplein 4 1020 Brussel Belgium	Prof Efira André	Comité d'éthique du CHU Brugmann
13	**Centre Hospitalier Peltzer - La Tourelle**	Rue du Parc 29 4800 Verviers Belgium	Dr Rezaei Kalantari Hassan	Comité d'éthique du CHR Verviers
14	**Hôpitaux Iris Sud – Ixelles**	J. Paquotstraat 63 1050 Brussel Belgium	Dr Kains Jean-Pierre	Comité d'Ethique des Hôpitaux Iris Sud
15	**Clinique Hospitalier Chrétien Saint-Joseph - Liège**	Rue de Hesbaye 75 4000 Liège Belgium	Dr Marie-Pascale Graas	Le Comité d'éthique médicale CHC Liège
16	**CHWAPI - Site IMC**	Chaussée de St-Amand, 80 7500 TOURNAI Belgium	Dr Kargar Khalil	Le Comité d'éthique du CHWAPI
17	**CHR - Mons (Saint-Joseph)**	Avenue B. de Constantinople 5 7000 Mons Belgium	Dr Dominique Boulet	Le Comité d'éthique CHR Mons-Hainaut
18	**CHBAH (Seraign)**	Rue Laplace 40 4100 Seraign Belgium	Dr Butenda Dominique	Le Comité d'éthique Centre Hospitalier Bois de L'abbaye
19	**CHBAH (Seraign)**	Rue Laplace 40 4100 Seraign Belgium	Dr Lampertz Serge	Le Comité d'éthique Centre Hospitalier Bois de L'abbaye
20	**Centre Hospitalier Emile Mayrisch**	Rue Emile Mayrisch L-4005 Esch-sur-alzette Grand Duchy of Luxembourg	Dr Stefan Rauh	Comité National d'ethique de Recherche Luxembourg

1.1.3. IEC in the Czech Republic

Multicentric Ethics Committee FN Brno , Fakultní nemocnice Brno, Jihlavská 28, Czech Republic

1.1.4. IECs/IRBs in Italy for the study XM22-ONC-40075

1. Comitato Etico
   Azienda Ospedaliera Universitaria

Città della Salute e della Scienza di Torino
Presidio Ospedaliero Molinette
Padiglione beige, 3° piano
Corso Bramante n. 88/90
10126 Torino

2. Comitato Etico Unico Regionale per la Basilicata
A.O.R. San Carlo
Via Potito Petrone s.n.c.
85100 Potenza
3. Comitato Etico Catania 1
Via Santa Sofia n. 78
95123 Catania
4. Comitato Etico ASL 1 Sassari
Via Monte Grappa n. 82
07100 Sassari
5. Comitato Etico Provinciale di Varese
Ospedale di Circolo e Fondazione Macchi
Viale L. Borri n. 57
21100 Varese
6. Comitato Etico A.O.R.N.
A.O.R.N. Antonio Cardarelli
Via A. Cardarelli n. 9
80131 Napoli
7. Comitato Etico Indipendente
Azienda Ospedaliero Universitaria di Cagliari
Via Ospedale n. 54
09124 Cagliari
8. Comitato Etico
Azienda Ospedaliera Universitaria Mater Domini
Campus Universitario "Salvatore Venuta" XI livello Stanza n. 8 - pad. B pre-clinico
Viale Europa - Località Germaneto
88100 Catanzaro
9. Comitato Etico Campania Sud
Servizio di Coordinamento
Piazza San Giovanni s.n.c.
80031 Brusciano (NA)
10. CE Area Vasta Centro
Azienda Ospedaliero-Universitaria di Careggi
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50134 Firenze
11. Comitato Etico
Azienda Ospedaliera Bianchi-Melacrino-Morelli
Via Provinciale Spirito Santo n. 28
89100 Reggio Calabria

12. Comitato Etico La Sapienza
Azienda Ospedaliera Policlinico Umberto I
Viale del Policlinico n. 155
00161 Roma
13 Comitato Etico Interregionale
Azienda Ospedaliera Policlinico di Bari
Piazza Giulio Cesare n. 11
70124 Bari
14. Comitato Etico Regionale delle Marche Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona Via Conca n. 71 – 60126 Torrette di Ancona
15. Comitato Etico
Seconda Università degli Studi di Napoli
A.O.U. SUN – A.O.R.N. Ospedali dei Colli
Via Leonardo Bianchi n. 1
80131 Napoli
16. Comitato Etico Area Vasta Nord Ovest
Via Roma n. 67
56126 Pisa
17. Comitato Etico
delle Province di Chieti e Pescara e
dell'Università degli Studi "G. D'Annunzio"
Via dei Vestini n. 29/B
66013 Chieti
18. Comitato Etico Interaziendale
Azienda Ospedaliera Santa Croce e Carle
Via Monte Zovetto n. 18
12100 Cuneo
19. Comitato Etico
Università Campus Bio-Medico di Roma
Via Álvaro del Portillo n. 21
00128 Roma
20. Comitato Etico Provinciale della Provincia di Brescia
Azienda Ospedaliera Spedali Civili
Piazzale Spedali Civili n. 1
25123 Brescia
21. Comitato Etico Lazio 1
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c/o Farmacia
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00152 Roma
22. Segreteria del Comitato Etico della provincia Monza Brianza
c/o Ufficio Sperimentazioni Cliniche
ASST Monza

Via Pergolesi n. 33
20900 MONZA (MI)

23. Comitato Etico IRCCS Pascale
Istituto Nazionale Tumori IRCCS - Fondazione Pascale
Via Mariano Semmola
80131 Napoli

1.1.5. IECs/IRBs in Italy for the study XM22-ONC-40084

- Comitato Etico Area Cremona Mantova e Lodi
- CER c/o Azienda Ospedaliero Universitaria “Ospedali Riuniti” di Ancona
- Comitato Etico delle Aziende Sanitarie dell’Umbria-CEAS Umbria
- Comitato Etico Catania 2
- Comitato Etico della provincia di Brescia
- Comitato Etico Interaziendale Azienda Ospedaliera “SS. Antonio e Biagio e C. Arrigo” di Alessandria
- Comitato Etico IRCCS Ospedale San Raffaele
- Comitato Etico Interaziendale della provincia di Messina
- Comitato Etico delle provincie di Chieti e Pescara
- Comitato Etico Lazio 2
- Comitato Etico dell’Università “La Sapienza”
- Comitato Etico CARDARELLI-SANTOBONO
- Comitato Etico “Campania Centro”
- Comitato Etico Indipendente Azienda Universitaria Ospedaliera Consorziale Policlinico di Bari
- Comitato Etico Degli Ospedali Riuniti Di Foggia
- Comitato Indipendente di etica medica ASL BR
- Comitato Etico Unico regionale per la Basilicata
- Sezione Del Ce Giovanni Paolo II - Bari C/O IRCCS Casa Sollievo Della Sofferenza
- Comitato Etico Azienda Ospedaliero Universitaria San Luigi Gonzaga
- Comitato Etico ASREM (Azienda Sanitaria Regionale del Molise)
- Comitato Etico dell’Università Campus Biomedico di Roma

1.1.6. IEC in Poland

Ethics Committee of the Krakow Medical Association at ul. Krupnicza 11A, Krakow

1.1.7. IEC in Slovakia

Ethics Committee of National Cancer Institute, 833 10 Bratislava, Klenova 1, Slovakia

1.1.8. IECs/IRBs in Spain

Classification AEMPS (Agencia Española del Medicamento y Productos Sanitarios) as Epa-SP: 06 October 2014 with approvals of the CCAA (Autonomous Communities):

- Approval by first committee (H. Ramón y Cajal): 12 December 2014
- Asturias: 13 May 2015
- Baleares: 10 November 2015
- Galicia: 31 March 2015 and 02 October 2015 for additional centres
- Pais Vasco: 05 May 2015

1.1.9. IECs/IRBs in The Netherlands

In the Netherlands observational studies do not need to be approved by an IEC, but by the workgroup non-WMO and the local board of directors of the participating hospitals. However, EC have been involved in the LEOS study advising the workgroup non-WMO and local board of directors.

Central Approval	Advised by Ethics committee
Initial submission: Codecommissie van de Stichting CGR (later Workgroup non-WMO)	Adviescommissie nWMO SLAZ (Sint Lucas Andreas Ziekenhuis)
Amendment: Codecommissie van de Stichting CGR (later Workgroup non-WMO)	Adviescommissie nWMO OLVG (Onze Lieve Vrouwe Gasthuis)

Local Approval	Advised by Ethics committee
Board of directors Alexander Monro Ziekenhuis	NA
Board of directors approval Rode Kruis Ziekenhuis	Commissie locale toetsing medisch onderzoek van het Rode Kruis Ziekenhuis
Board of directors approval LUMC	Commissie Medische Ethiek (CME) van het LUMC
Board of directors approval Tjongerschans	NA
Board of directors approval Spaarne Gasthuis	Adviescommissie locale uitvoerbaarheid
Board of directors approval Ijsselland Ziekenhuis	NA
Board of directors approval Isala Diaconessenhuis	NA
Board of directors approval Noord West Ziekenhuisgroep	Bureau Wetenschap

1.2. Ethical conduct of the study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the Declaration of Helsinki.

1.3. Subject information and consent

Written informed consent was obtained prior to inclusion in the study. Electronic case report forms (eCRFs) were provided for each patient's data to be recorded.

Following the amendment #4 (dated 1st December 2015) of the clinical study protocol template (dated 1st August 2014), informed consent had to be obtained before any data collection and any procedures, including CT administration in the first chemotherapy cycle within this study. Prior to this amendment some patients signed ICF before Lonquex administration, but after CT administration. This was considered minor protocol violation and these patients were still included in the analysis.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

The studies included in this report were conducted by 142 investigators, in 114 centres, distributed in 9 European countries (Austria, Belgium, Czech Republic, Italy, Luxembourg, Poland, Slovakia, Spain, The Netherlands) (Table 1 to Table 3).

The protocol number are listed here below:

Protocol number	Country
TV44689-ONC-40101	Austria
XM22-ONC-40080	Belgium/Luxembourg
XM22-ONC-40094	Czech Republic
XM22-ONC-40075	Italy Levity
XM22-ONC-40084	Italy Perla
XM22-ONC-40078	Poland
XM22-ONC-40093	Slovakia
XM22-ONC-40072	Spain
XM22-ONC-40081	The Netherlands

Table 1 Distribution of patients in the nine participating European countries (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Austria	*241*	*18.4*	*18.4*	*18.4*
	Belgium	*137*	*10.4*	*10.4*	*28.8*
	Czech Republic	*68*	*5.2*	*5.2*	*34.0*
	Italy	*486*	*37.0*	*37.0*	*71.0*
	Luxembourg	*2*	*.2*	*.2*	*71.1*
	Poland	*155*	*11.8*	*11.8*	*82.9*
	Slovakia	*78*	*5.9*	*5.9*	*88.9*
	Spain	*4*	*.3*	*.3*	*89.2*
	The Netherlands	*142*	*10.8*	*10.8*	*100.0*
	Total	*1313*	*100.0*	*100.0*	

Table 2 Distribution of patients in the different participating centres (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A. O. S. Carlo-Potenza	24	1.8	1.8	1.8
	A. O. S. Maria	8	.6	.6	2.4
	A.O Ospedali Riuniti Marche Nord	10	.8	.8	3.2
	A.O. S. Andrea	9	.7	.7	3.9
	A.O. Sant'Andrea	12	.9	.9	4.8
	A.O. SS. Annunziata	28	2.1	2.1	6.9
	A.O.R.N. Antonio Cardarelli	18	1.4	1.4	8.3
	A.O.R.N. Cardarelli	2	.2	.2	8.5
	A.O.U. Consorziale Policlinico di Bari	17	1.3	1.3	9.7
	A.R.N.A.S. Garibaldi	13	1.0	1.0	10.7
	Alexander Monro Ziekenhuis	19	1.4	1.4	12.2
	Ambulatorium Chemioterapii	18	1.4	1.4	13.6
	AOU “Ospedali Riuniti” di Ancona	14	1.1	1.1	14.6
	AOU CAREGGI	8	.6	.6	15.2
	AOU San Luigi Gonzaga	9	.7	.7	15.9
	ASL 3 Nuoro	9	.7	.7	16.6
	ASL AT di Asti	2	.2	.2	16.8
	ASL di Salerno	2	.2	.2	16.9
	ASST VIMERCATE	8	.6	.6	17.5
	Asur Area Vasta n. 4 Fermo	9	.7	.7	18.2
	AZ Damiaan	10	.8	.8	19.0
	AZ Maria Middelares	14	1.1	1.1	20.0
	AZ Monica – UZA	3	.2	.2	20.3
	AZ Sint Jan Brugge - Oostende	26	2.0	2.0	22.2
	AZ Sint-Rembert	3	.2	.2	22.5
	Az. Osp.Universitaria di Sassari	10	.8	.8	23.2
	Az. Sanitaria Provinciale di Ragusa	3	.2	.2	23.5
	Azienda dei Colli	16	1.2	1.2	24.7
	Azienda Ospedaliera "Bianchi-Melacrino-Morelli"	5	.4	.4	25.1
	Azienda Ospedaliera Brotzu	3	.2	.2	25.3
	Azienda Ospedaliera di Perugia	15	1.1	1.1	26.4
	Campus Bio-Medico	25	1.9	1.9	28.3
	Center1	16	1.2	1.2	29.6
	Center2	10	.8	.8	30.3

		Frequency	Percent	Valid Percent	Cumulative Percent
	Center3	*11*	*.8*	*.8*	*31.2*
	Center4	*11*	*.8*	*.8*	*32.0*
	Center6	*9*	*.7*	*.7*	*32.7*
	Center8	*11*	*.8*	*.8*	*33.5*
	Centre Hospitalier Emile Mayrisch	*2*	*.2*	*.2*	*33.7*
	Centre Hospitalier Peltzer - La Tourelle	*6*	*.5*	*.5*	*34.1*
	CHBAH – Butenda	*1*	*.1*	*.1*	*34.2*
	CHR St-Joseph Mons	*1*	*.1*	*.1*	*34.3*
	CHU Brugmann - Victor Horta	*4*	*.3*	*.3*	*34.6*
	Chwapi	*17*	*1.3*	*1.3*	*35.9*
	Clinique Saint-Joseph Liège	*18*	*1.4*	*1.4*	*37.2*
	CMSE Namur	*10*	*.8*	*.8*	*38.0*
	Dzienny Oddzial Chemioterapii	*10*	*.8*	*.8*	*38.8*
	Faculty hospital Trnava	*3*	*.2*	*.2*	*39.0*
	Faculty hospital Trnava 2	*5*	*.4*	*.4*	*39.4*
	Faculty HospitalNitra	*3*	*.2*	*.2*	*39.6*
	FNsP Banská Bystrica	*6*	*.5*	*.5*	*40.1*
	Fondazione Poliambulanza	*5*	*.4*	*.4*	*40.4*
	Hanusch Krankenhaus. Brustzentrum	*5*	*.4*	*.4*	*40.8*
	Hematologia Košice	*6*	*.5*	*.5*	*41.3*
	Hôpitaux Iris Sud	*3*	*.2*	*.2*	*41.5*
	Hosp. Begoña	*1*	*.1*	*.1*	*41.6*
	IFO – Istituto Regina Elena IRCCS	*14*	*1.1*	*1.1*	*42.7*
	Ijsselland ziekenhuis	*15*	*1.1*	*1.1*	*43.8*
	IRCCS Casa Sollievo della Sofferenza	*17*	*1.3*	*1.3*	*45.1*
	IRCCS CROB	*22*	*1.7*	*1.7*	*46.8*
	Isala Meppel	*4*	*.3*	*.3*	*47.1*
	Ist. Nazionale Tumori - Pascale	*6*	*.5*	*.5*	*47.5*
	istituti Ospitalieri di Cremona	*8*	*.6*	*.6*	*48.1*
	Klinika Chorób Wewnetrznych Hematologii i Onkologii	*20*	*1.5*	*1.5*	*49.7*
	Klinika Gastroenterologii	*19*	*1.4*	*1.4*	*51.1*
	Klinika Hematologii	*13*	*1.0*	*1.0*	*52.1*
	Klinika Hematologii i Transplantacji Szpiku	*7*	*.5*	*.5*	*52.6*
	Klinika Nowotworów Ukladu Chlonnego	*18*	*1.4*	*1.4*	*54.0*
	Klinika Onkologii i Chorób Wewnetrznych	*2*	*.2*	*.2*	*54.2*

		Frequency	Percent	Valid Percent	Cumulative Percent
	Krankenhaus der Barmherzigen Brüder Salzburg	***11***	***.8***	***.8***	***55.0***
	Krankenhaus Schwarzach	***20***	***1.5***	***1.5***	***56.5***
	Leids Universitair Medisch Centrum	***5***	***.4***	***.4***	***56.9***
	LKH Hochsteiermark – Standort Leoben	***4***	***.3***	***.3***	***57.2***
	Mammacentrum Sv. Agáty	***5***	***.4***	***.4***	***57.6***
	Martinská fakultná nemocnica	***7***	***.5***	***.5***	***58.1***
	Medizin. Universität Graz	***45***	***3.4***	***3.4***	***61.5***
	Medizinische Universität Wien	***53***	***4.0***	***4.0***	***65.6***
	Národný Onkologický Ustav Bratislava 2	***3***	***.2***	***.2***	***65.8***
	Noordwestgroep Alkmaar	***19***	***1.4***	***1.4***	***67.3***
	Oddzial Chemioterapii	***10***	***.8***	***.8***	***68.0***
	Oddzial Hematologii	***5***	***.4***	***.4***	***68.4***
	Oddzial Hematologii Onkologicznej	***10***	***.8***	***.8***	***69.2***
	Oddzial Kliniczny Onkologii	***22***	***1.7***	***1.7***	***70.8***
	Oddzial Radioterapii i Onkologii Klinicznej	***1***	***.1***	***.1***	***70.9***
	Onkologia Komárno	***3***	***.2***	***.2***	***71.1***
	Onkológia. NsP Trebišov	***3***	***.2***	***.2***	***71.4***
	Onkológia. NsP Trebišov 2	***3***	***.2***	***.2***	***71.6***
	Onkologická ambulancia Nádej	***11***	***.8***	***.8***	***72.4***
	Onkologický ústav Košice 2	***4***	***.3***	***.3***	***72.7***
	Onkologický ústav Sv. Alžbety	***7***	***.5***	***.5***	***73.3***
	Onkomed BB Banská Bystrica	***3***	***.2***	***.2***	***73.5***
	Ospedale C. e G. Mazzoni	***3***	***.2***	***.2***	***73.7***
	Ospedale Civile Santo Spirito	***5***	***.4***	***.4***	***74.1***
	Ospedale di Circolo e Fondazione Macchi	***7***	***.5***	***.5***	***74.6***
	Ospedale generale provinciale di Macerata	***2***	***.2***	***.2***	***74.8***
	Ospedale Monsignor R. Dimiccoli	***19***	***1.4***	***1.4***	***76.2***
	Ospedale S. Eugenio-Roma	***8***	***.6***	***.6***	***76.8***
	Ospedale San Raffaele	***10***	***.8***	***.8***	***77.6***
	Ospedale San Vincenzo	***5***	***.4***	***.4***	***78.0***
	P.O. Lamezia Terme	***14***	***1.1***	***1.1***	***79.1***
	P.O. San Gennaro	***7***	***.5***	***.5***	***79.6***
	Policlínica Lucense	***3***	***.2***	***.2***	***79.8***
	Policlinico Universitario Campus Biomedico	***9***	***.7***	***.7***	***80.5***
	Presidio Ospedaliero Molinette	***31***	***2.4***	***2.4***	***82.9***
	Private ordination	***45***	***3.4***	***3.4***	***86.3***

		Frequency	Percent	Valid Percent	Cumulative Percent
	Rode Kruis Ziekenhuis	***23***	***1.8***	***1.8***	***88.0***
	Spaarne gasthuis	***43***	***3.3***	***3.3***	***91.3***
	Spedali Civili di Brescia	***10***	***.8***	***.8***	***92.1***
	SS. Antonio e Biagio e Cesare Arrigo	***5***	***.4***	***.4***	***92.5***
	Tjongerschans	***14***	***1.1***	***1.1***	***93.5***
	UN Sv. Cyrila a Metoda Bratislava	***5***	***.4***	***.4***	***93.9***
	Universitätsklinikum St. Pölten	***58***	***4.4***	***4.4***	***98.3***
	University Hospital Bratislava	***1***	***.1***	***.1***	***98.4***
	UZ Brussel	***21***	***1.6***	***1.6***	***100.0***
	Total	***1313***	***100.0***	***100.0***	

Table 3 Distribution of patients among the study investigators (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	[redacted]	2	.2	.2	.2
	[redacted]	4	.3	.3	.5
	[redacted]	2	.2	.2	.6
	[redacted]	18	1.4	1.4	2.0
	[redacted]	21	1.6	1.6	3.6
	[redacted]	9	.7	.7	4.3
	[redacted]	1	.1	.1	4.3
	[redacted]	1	.1	.1	4.4
	[redacted]	2	.2	.2	4.6
	[redacted]	8	.6	.6	5.2
	[redacted]	5	.4	.4	5.6
	[redacted]	13	1.0	1.0	6.5
	[redacted]	3	.2	.2	6.8
	[redacted]	6	.5	.5	7.2
	[redacted]	4	.3	.3	7.5
	[redacted]	1	.1	.1	7.6
	[redacted]	10	.8	.8	8.4
	[redacted]	6	.5	.5	8.8
	[redacted]	4	.3	.3	9.1
	[redacted]	3	.2	.2	9.4
	[redacted]	1	.1	.1	9.4
	[redacted]	10	.8	.8	10.2
	[redacted]	3	.2	.2	10.4
	[redacted]	1	.1	.1	10.5
	[redacted]	17	1.3	1.3	11.8
	[redacted]	2	.2	.2	12.0
	[redacted]	2	.2	.2	12.1
	[redacted]	2	.2	.2	12.3
	[redacted]	7	.5	.5	12.8
	[redacted]	18	1.4	1.4	14.2
	[redacted]	3	.2	.2	14.4
	[redacted]	1	.1	.1	14.5
	[redacted]	1	.1	.1	14.5
	[redacted]	3	.2	.2	14.8
	[redacted]	3	.2	.2	15.0
	[redacted]	26	2.0	2.0	17.0

	Frequency	Percent	Valid Percent	Cumulative Percent
[redacted]	18	1.4	1.4	18.4
[redacted]	10	.8	.8	19.1
[redacted]	16	1.2	1.2	20.3
[redacted]	2	.2	.2	20.5
[redacted]	4	.3	.3	20.8
[redacted]	1	.1	.1	20.9
[redacted]	2	.2	.2	21.0
[redacted]	5	.4	.4	21.4
[redacted]	14	1.1	1.1	22.5
[redacted]	25	1.9	1.9	24.4
[redacted]	14	1.1	1.1	25.4
[redacted]	8	.6	.6	26.0
[redacted]	5	.4	.4	26.4
[redacted]	20	1.5	1.5	28.0
[redacted]	5	.4	.4	28.3
[redacted]	10	.8	.8	29.1
[redacted]	8	.6	.6	29.7
[redacted]	10	.8	.8	30.5
[redacted]	14	1.1	1.1	31.5
[redacted]	3	.2	.2	31.8
[redacted]	2	.2	.2	31.9
[redacted]	8	.6	.6	32.5
[redacted]	8	.6	.6	33.1
[redacted]	14	1.1	1.1	34.2
[redacted]	10	.8	.8	35.0
[redacted]	4	.3	.3	35.3
[redacted]	19	1.4	1.4	36.7
[redacted]	9	.7	.7	37.4
[redacted]	2	.2	.2	37.5
[redacted]	9	.7	.7	38.2
[redacted]	6	.5	.5	38.7
[redacted]	5	.4	.4	39.1
[redacted]	10	.8	.8	39.8
[redacted]	7	.5	.5	40.4
[redacted]	1	.1	.1	40.4
[redacted]	14	1.1	1.1	41.5
[redacted]	8	.6	.6	42.1
[redacted]	7	.5	.5	42.7

	Frequency	Percent	Valid Percent	Cumulative Percent
[redacted]	4	.3	.3	43.0
[redacted]	5	.4	.4	43.3
[redacted]	23	1.8	1.8	45.1
[redacted]	1	.1	.1	45.2
[redacted]	2	.2	.2	45.3
[redacted]	19	1.4	1.4	46.8
[redacted]	5	.4	.4	47.1
[redacted]	7	.5	.5	47.7
[redacted]	10	.8	.8	48.4
[redacted]	2	.2	.2	48.6
[redacted]	2	.2	.2	48.7
[redacted]	18	1.4	1.4	50.1
[redacted]	6	.5	.5	50.6
[redacted]	6	.5	.5	51.0
[redacted]	6	.5	.5	51.5
[redacted]	3	.2	.2	51.7
[redacted]	8	.6	.6	52.3
[redacted]	17	1.3	1.3	53.6
[redacted]	9	.7	.7	54.3
[redacted]	8	.6	.6	54.9
[redacted]	9	.7	.7	55.6
[redacted]	28	2.1	2.1	57.7
[redacted]	58	4.4	4.4	62.1
[redacted]	3	.2	.2	62.4
[redacted]	17	1.3	1.3	63.7
[redacted]	5	.4	.4	64.1
[redacted]	3	.2	.2	64.3
[redacted]	17	1.3	1.3	65.6
[redacted]	13	1.0	1.0	66.6
[redacted]	16	1.2	1.2	67.8
[redacted]	9	.7	.7	68.5
[redacted]	1	.1	.1	68.5
[redacted]	12	.9	.9	69.5
[redacted]	10	.8	.8	70.2
[redacted]	19	1.4	1.4	71.7
[redacted]	3	.2	.2	71.9
[redacted]	2	.2	.2	72.0
[redacted]	11	.8	.8	72.9

	Frequency	Percent	Valid Percent	Cumulative Percent
[redacted]	5	.4	.4	73.3
[redacted]	11	.8	.8	74.1
[redacted]	3	.2	.2	74.3
[redacted]	10	.8	.8	75.1
[redacted]	11	.8	.8	75.9
[redacted]	3	.2	.2	76.2
[redacted]	3	.2	.2	76.4
[redacted]	11	.8	.8	77.2
[redacted]	11	.8	.8	78.1
[redacted]	9	.7	.7	78.8
[redacted]	31	2.4	2.4	81.1
[redacted]	6	.5	.5	81.6
[redacted]	11	.8	.8	82.4
[redacted]	3	.2	.2	82.6
[redacted]	7	.5	.5	83.2
[redacted]	5	.4	.4	83.5
[redacted]	3	.2	.2	83.8
[redacted]	3	.2	.2	84.0
[redacted]	1	.1	.1	84.1
[redacted]	16	1.2	1.2	85.3
[redacted]	4	.3	.3	85.6
[redacted]	7	.5	.5	86.1
[redacted]	6	.5	.5	86.6
[redacted]	5	.4	.4	87.0
[redacted]	5	.4	.4	87.4
[redacted]	4	.3	.3	87.7
[redacted]	11	.8	.8	88.5
[redacted]	8	.6	.6	89.1
[redacted]	45	3.4	3.4	92.5
[redacted]	98	7.5	7.5	100.0
Total	1313	100.0	100.0	

3. INTRODUCTION

Use of chemotherapy (CT) can be limited by dose limiting toxicities that may delay subsequent treatment cycles. One of the most common toxicities is neutropenia which, although asymptomatic, is associated with many clinically important complications, including febrile neutropenia (FN). The risk of initial infection and subsequent complications is inversely proportional to the absolute neutrophil count (ANC), and begins to increase when ANC is $<1.5 \times 10^9$/L; consequently, the National Cancer Institute has defined neutropenia as $<1.0 \times 10^9$/L [1]. Recombinant granulocyte colony stimulating factor (G-CSF) products have emerged as effective therapies for reducing the duration and incidence of chemotherapy induced neutropenia (CIN) and FN by stimulating neutrophil production and differentiation [2,3]. Short acting recombinant N-methionyl form of human granulocyte colony stimulating factor (r-metHuG-CSFs) products, such as filgrastim require daily subcutaneous (s.c.) injections during each CT cycle. The attachment of a polyethylene glycol (PEG) molecule (pegylation) to filgrastim (e.g., pegfilgrastim) decreases plasma clearance and extends the drug's half-life in the body, while having no impact on the safety profile, allowing for less-frequent dosing [4,5]. It is recommended that administration of pegfilgrastim is not less than 24 hours following CT [6,7], with recovery of ANC to normal levels having been shown to correlate with decline of pegfilgrastim concentrations [8].

Lonquex® (International Nonproprietary Name lipegfilgrastim) is a glycoPEGylated formulation of r-metHuG-CSF that has been developed for the prevention of CIN. It received European Union (EU) marketing approval on 25 July 2013 for the indication "Reduction in the duration of neutropenia and the incidence of FN in adult patients treated with cytotoxic CT for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)".

The natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids and is glycosylated at threonine 133. G-CSF regulates the proliferation and differentiation of progenitor cells within the bone marrow and the release of mature neutrophils into the peripheral blood, is a positive regulator of granulopoiesis, acting at different stages of myeloid cell development, and enhances the effector functions of normal mature neutrophils, including chemotaxis, phagocytosis and oxidative metabolism, exerting its effects via a high-affinity G-CSF specific receptor mechanism, which accounts for its selective action compared to many other cytokines.

Lonquex® is produced by site specific enzyme mediated covalent attachment of a single 20 kDa mPEG molecule via a glycolinker to the natural O-glycosylation site at threonine 134 of recombinant r-metHuG-CSF. By means of this glycoPEGylation the pharmacodynamic effect is prolonged compared to filgrastim.

TEVA has performed these post-authorization studies primarily to describe the effect of the long-acting G-CSF therapy Lonquex® (Lipegfilgrastim), used in prophylaxis, on delay of CT use, CT dose omissions and reduction in CT dose in patients receiving cytotoxic CT for solid and haematological malignancies.

4. STUDY OBJECTIVES

4.1. Primary objective

The primary objective of this Phase IV study was to describe the effect of the long-acting G-CSF therapy Lonquex® (Lipegfilgrastim) used in prophylaxis on CT, and specifically, on delay of CT use, CT dose omissions and reduction in CT dose in patients receiving cytotoxic CT for solid and haematological malignancies, according to routine clinical practice.

4.2. Secondary objectives

The secondary objectives were to document:

- Description of the population of cancer patients treated prophylactically by lipegfilgrastim in terms of their baseline characteristics: (1) tumour type and stage, (2) CT regimen and use (i.e., adjuvant or metastatic), (3) Multinational Association of Supportive Care in Cancer (MASCC) Index score, (4) demographics including gender, age, ethnicity and performance status (PS), (5) co-morbidities and (6) FN risk 10-20% with additional risk or >20%.
- Description of effect on QoL and pain as measured by Brief Pain Inventory (BPI) and EORTC QLQ-C30.

5. INVESTIGATIONAL PLAN

5.1. Study design

- Multicentre, prospective, observational cohort study of cancer patients receiving cytotoxic CT and Lonquex® in outpatient and inpatient setting.
- Lonquex® has been administered at discretion of the physician.
- Patients have been followed for the cycles in which Lonquex® was administered as either primary or secondary prophylaxis of neutropenia, during the chemotherapy regimen, until 6 to 8 weeks after the last dose of lipegfilgrastim.
- The studies included in this report have been performed in Austria, Belgium, Czech Republic, Italy, Luxembourg, Poland, Slovakia, Spain and The Netherlands.
- Completion of a study screening including patients' demographics and baseline data such as date of birth, planned CT regimen, additional FN risk factors were captured.
- In addition whether they receive G-CSF in primary prophylaxy (PP) or secondary prophylaxy (SP) was documented.
- For each cycle, chemotherapy (CT) and biological therapy (BT) treatment data was captured. CT and BT were administered at the discretion of the physician.
- After the last dose of lipegfilgrastim a last data collection was to be done after 6 to 8 weeks.
- All data were captured in an eCRF.
- Completion of informed patient consent and signed consent forms was mandatory prior to inclusion in the study.

5.2. Study procedures

The study procedures and assessments are summarized in Table 4.

Table 4 Outline of study procedures and assessments

	Screening log	Baseline	Treatment cycles		End of study 6 to 8 weeks after last dose of Lonquex®
			Each cycle	Additional at first day of last cycle	
Informed consent	●				
Patient identification number	●				
Demographics	●				
Tumour characteristics (type and stage)	● Type	● Stage			
Risk factors for FN	●				
CT regimen	●	●			
G-CSF prophylaxis planned + type	●	●			
Inclusion/Exclusion criteria	●				
Medical history (including FN)		●			
Co-morbidities		●			
ECOG performance status (PS)		●			
History of FN without antibiotic nor G-CSF prophylaxis		●			
Nutritional deficiency		●			
Diagnosis date		●			
Previous treatment for cancer		●			
MASCC score*			●*		
FN risk (Investigator's assessed)		●			
Planned CT and/or BT (adjuvant or metastatic)		●			
Use of Lonquex® (including day of cycle)		●	●		
EORTC-QLQ-C30		●		●	●
BPI		●		●	●
CT timing/delay/omission			●		
CT dose			●		
BT dose/omission/reduction			●		
Febrile neutropenia or neutropenia in previous cycle			●		●
Use of anti-infectives and anti-mycotics			●		●
Hospitalisation (nb of days and reason)			●		●
Blood transfusion (nb of units)			●		●
Culture-confirmed infection (in case of AE only)			●		●
AEs/SAEs/ADRs/SADRs/Pregnancy			●		●
Study conclusion					●

*In case of Febrile Neutropenia the MASCC score is calculated. BT = biological treatment, BPI = Brief Pain Inventory, CT = chemotherapy, EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer, FN = febrile neutropenia, G-CSF = granulocyte-colony stimulating factor, MASCC = Multinational Association of Supportive Care in Cancer, PS = performance status

5.2.1. Screening

- Signed and dated informed consent form. Informed consent has to be obtained before any data collection and any procedures, including CT administration in the first chemotherapy cycle within this study.
- Inclusion/Exclusion criteria
- Patient identification number assignment: 2 letters for the country code, followed by 5 to 6 digits (2 to 3 digits for the centre and 3 digits for the patient), separated by hyphens.
- Demographics including date of birth (to derive the age), gender and ethnicity
- Tumour type
- Risk factors for FN

5.2.2. Baseline

- Stage of tumour
- Co-morbidities
- ECOG Performance Status
- History of FN without antibiotic prophylaxis nor G-CSF prophylaxis
- Nutritional deficiency
- Diagnosis date
- Previous treatment for cancer
- FN risk (Investigator's assessed FN risk based on received CT and patient's characteristics)
- Planned CT
- Adjuvant or metastatic use of CT and CT schedule
- Planned biological/targeted treatment and their setting (adjuvant or metastatic)
- Use of Lonquex® in PP or SP. In SP, the CT or biological cancer treatment given just before inclusion in the trial will also be documented
- EORTC QLQ-C30
- BPI

5.2.3. At each cycle

- Use of Lonquex® (including day of cycle)
- CT timing/delay/omission
- CT dose

- BT dose/omission/reduction
- FN or neutropenia in previous cycle
- Use of anti-infectives and anti-mycotics
- Hospitalisation (number of days and reason)
- Blood transfusion (number of units)
- Culture-confirmed infection (in case of AE only)
- AEs/SAEs/ADRs/SADRs/Pregnancy
- MASCC score (if applicable)

5.2.4. First day of last cycle

In addition to the procedures of Section 5.2.3, the following variables were recorded:

- EORTC-QLQ-C30
- BPI

5.2.5. End of study: 6-8 weeks after last dose of Lonquex®

- FN or neutropenia in the last chemotherapy cycle
- Use of anti-infectives and anti-mycotics
- Hospitalisation (number of days and reason)
- Blood transfusion (number of units)
- EORTC-QLQ-C30
- BPI
- AEs/SAEs/ADRs/SADRs/Pregnancy
- Study conclusion

5.3. Selection of study population

The study population consisted of male and female cancer patients aged ≥18 years, receiving cytotoxic CT or BT for solid or haematological malignancies, and receiving prophylactic G-CSF treatment with Lonquex®.

If the patient fulfilled all study inclusion and exclusion criteria, he/she was included in the study.

5.3.1. Inclusion criteria

Patients could be included in the study only if they meet all of the following criteria:

- Adult cancer patient ≥18years.
- Patient receiving Lonquex® for PP or SP of CIN.
- Signature of a written informed consent document.

5.3.2. Exclusion criteria

Patients were excluded from participating in this study if they met any of the following criteria:

- Participation in another clinical trial that investigated study drug that was not yet marketed.
- Patients with chronic myeloid leukaemia and myelodysplastic syndromes.
- The patient was a pregnant or lactating woman.

5.3.3. Subject completion and withdrawal from study

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient was free to withdraw from the observational study at any time. Should a patient decide to withdraw, or should the physician decide to withdraw the patient, all efforts were to be made to complete and report all observations up to the time of withdrawal.

The reason for and date of withdrawal was recorded on the source documentation and transcribed onto the eCRF (study conclusion). If a patient withdrew consent, every attempt was made to determine the reason. If the reason for withdrawal was an AE or a clinically significant abnormal laboratory test result, monitoring was to be continued at the discretion of the physician (e.g., until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result(s) had to be recorded on the source documentation and transcribed onto the eCRF. If a patient withdrew from the study for multiple reasons that included AEs, details recorded in the eCRF should indicate that the withdrawal was related to an AE.

5.4. Composition and administration of study drug

5.4.1. Description of study drug

Lonquex® (lipegfilgrastim) was administered at discretion of the physician in line with marketing authorization as defined in the Summary of Product Characteristics (SmPC) of Lonquex®.

5.4.2. Dosage and administration

Dosage of Lonquex was 6 mg administered once per cycle (SmPC of Lonquex®).

5.4.3. Treatment allocation and randomization

Not applicable, this was an open observational study.

5.4.4. Blinding

Not applicable, this was an open observational study.

5.5. Prior and concomitant medication

CT and BT were administered at the discretion of the physician.

In each cycle, it was recorded if anti-infectives and anti-mycotics were administered. However, no generic or trade names were collected.

Generic or trade name, indication, and dosage of all concomitant medications were recorded only in case of adverse events and were reported in AE/SAE form.

5.6. Assessment of safety variables

5.6.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any AE occurring after the study patient has signed the informed consent form should be recorded and reported as an AE.

An AE can, therefore, be any unfavourable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study were not considered AEs.

Accordingly, an AE could include any of the following:

- Intercurrent illnesses
- Physical injuries
- Events possibly related to concomitant medication
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that was intermittently symptomatic [e.g., headache] and which occurred during the study should be recorded as an AE.)

- Drug interactions
- Events occurring during diagnostic procedures or during any washout phase of the study
- Laboratory or diagnostic test abnormalities that resulted in the withdrawal of the patient from the study, were associated with clinical signs and symptoms or a SAE, or required medical treatment or further diagnostic work-up, or were considered by the physician to be clinically significant. All events of possible drug-induced liver injury with hyperbilirubinaemia (defined as aspartate aminotransferase or alanine aminotransferase ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or International Normalized Ratio >1.5) or Hy's Law events required immediate study treatment cessation and reporting as a SAE.

Clinically relevant was considered non-responding to the treatment with Lonquex® as most biological medicinal products elicit some level of anti-drug antibody response. This antibody response could, in some cases, lead to undesirable effects or loss of efficacy. If a patient failed to respond to treatment, the patient should undergo further evaluation. If there was a suspicion of lack of efficacy due to immunogenicity/anti-drug-antibody reaction, the sponsor´s pharmacovigilance (PhV) should be contacted.

5.6.2. Adverse Drug Reaction

- An adverse drug reaction is defined as a response to a medicinal product which is noxious and unintended.
- Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
- Adverse reactions could arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

5.6.3. Recording and reporting adverse events

For AE recording, the study period was defined for each patient as that time period from signature of the informed consent form through the end of the follow-up period. For this study, the follow-up period was defined as 6-8 weeks after last cycle with administration of Lonquex®.

Serious and non-serious AEs, including special situations, which occurred during the study period and which were recorded in the patient's medical records or source documentation must be transcribed onto the eCRF in the AE/SAE form, regardless of the severity of the event.

Very common chemotherapy-derived AE's were exempt from recording in the eCRF and reporting to pharmacovigilance. These AE's were the typical, common events associated with the chemotherapy regimen. The AEs that are exempt from recording in the eCRF were:

- Nausea and vomiting,
- Alopecia,
- Diarrhoea and constipation,
- Fatigue,
- Asthenia,
- (Neuropathic) pain,
- Hand-foot-syndrome,
- Swelling,
- Mouth sores,
- Appetite changes,
- Nervous system effects only if related to chemotherapy treatment,
- Cognitive changes or dysfunction only if related to chemotherapy treatment.

These chemotherapy-derived AEs had to be collected in the eCRF if the presentation and/or outcome was more severe, and/or more important, and/or the occurrence was more frequent than would be expected from the treatment, the SmPC or the medical condition. If such AE/SAE were also assessed as serious or related AEs, they were to be reported to PhV.

All other AEs not listed here were to be recorded in the eCRF in the AE/SAE form.

For AEs for which the protocol provided differently and did not require their systematic collection, healthcare professionals and consumers could report adverse reactions (for which a causal role of a medicine was suspected) to the marketing authorization holder of the suspected medicinal product (studied or not) or to the concerned competent authorities via the national spontaneous reporting system. In case of **SAEs** and **non-serious ADRs** (defined as non-serious AEs being considered by the physician as having a reasonable possibility of being related to Lonquex®), the AE/SAE Form in the eCRF had to be completed and had to be reported to the local safety officer (LSO). The clinical course of each AE had to be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient was referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure was made.

The onset and end dates, duration (in case of AE duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each AE had to be recorded on the source documentation and transcribed onto the eCRF.

The relationship of each AE to study drug treatment and study procedures, and the severity and seriousness of each AE, as judged by the physician, had to be recorded as described below.

5.6.4. Severity of an adverse event

The severity of each AE was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, current version 4.0 (NCI CTCAE version 4).

AEs that were not included in the NCI CTCAE lists were graded according to the NCI CTCAE general guideline for grades as follows:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2:** Moderate; minimal, local intervention, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated
- **Grade 5:** Death related to AE

5.6.5. Relationship of an adverse event to the study drug

The relationship of an AE to the study drug was characterized as in Table 5.

Table 5 Assessment of the relationship of an AE to the study drug

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc…) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.

Term	Definition	Clarification
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

In the eCRF following categories for assessment of relationship were used: Probable - Possible - Unlikely - Not assessable - Not related.

The Categories Probable - Possible - Unlikely - Not assessable were considered as reasonable possibility.

5.6.6. Serious adverse events

A SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

- Death
- A life threatening AE (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered SAEs.
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization;

or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE that does not meet any of the criteria for seriousness listed above was regarded as a non-serious AE.

5.6.7. Reporting a SAE and non-serious ADR

To satisfy regulatory requirements, all SAEs, regardless of judged relationship to treatment with Lonquex® and non-serious ADRs that occurred during the study period (including the 6 to 8 week after last cycle, protocol defined follow up period), had to be reported to the sponsor by the physician. The event had to be reported within 24 hours of when the physician learned about it. Completing the AE/SAE form in the eCRF and reporting the event could not be delayed, even if not all the information was available. The physician did not need to actively monitor patients for AEs once the study had ended. SAEs occurring to a patient after the treatment of that patient had ended had to be reported to the sponsor if the physician became aware of them.

The AE/SAE form was sent to the LSO or other designated personnel; the LSO forwarded the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

Each report of a SAE was reviewed and evaluated by the physician and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures and to underlying disease.

Additional information (follow up) about any SAE or non-serious ADR unavailable at the initial reporting was forwarded by the physician within 24 hours of when it became known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department had to distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities, IEC and physicians, according to regulations.

5.6.8. Protocol defined AEs NOT for reporting to pharmacovigilance

Neutropenia and FN were not actively reported to Pharmacovigilance as it was to be documented and collected as study variable. Therefore all AEs reporting neutropenia or FN should not be reported to the PhV department as they were to be documented and recorded in the eCRF of this study. Neutropenia and FN had to be recorded in the AE/SAE form in eCRF ONLY if there was suspicion of lack of efficacy due to immunogenicity/anti-drug-antibody reaction; or if the event was more severe and/or more important, or/and occurrence was more frequent than it would be expected. If such AE/SAE were also assessed as serious or related AEs they were to be reported to PhV.

Chemotherapy derived AEs were exempt from collection in the eCRF and reporting to pharmacovigilance. They had to be collected in the eCRF if the presentation and/or outcome was more severe, and/or more important, and/or the occurrence was more frequent than would be expected. If such AEs/SAEs were also assessed as serious or related AEs, they were to be reported to PhV.

Disease progression had to be recorded in the AE/SAE form in eCRF. It was to be reported to Pharmacovigilance only if assessed as serious or related AE.

5.6.9. Pregnancy

All pregnancies that occurred during the study, or within 14 days of completion of the study, were to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the physician had to provide the LSO with the Pregnancy form. A paper version of this form was provided. The process for reporting a pregnancy was the same as that for reporting an SAE.

All patients who became pregnant were to be monitored to the completion or termination of the pregnancy. If the pregnancy continued to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and new-born complications, were to be reported to the sponsor. Any complication of pregnancy was to be reported as an AE or SAE, as appropriate. For pregnancies of partners of men participating in the study, the PhV Department had to determine the procedure to appropriately follow up after notification as described above. All partners who became pregnant and provide appropriate consent to PhV were to be monitored to the completion or termination of the pregnancy.

If the pregnancy did not continue to term, one of the following actions was to be taken:

- For a spontaneous abortion, report a SAE.
- For an elective abortion due to developmental anomalies, report as a SAE.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form.

Information about pregnancies was collected following the Amendment#4, and only for patients who still did not complete End of Study visit at that time point.

5.6.10. Special situations

All special situations, as defined below, which occurred during the defined study period, were to be recorded on the source documentation and transcribed onto the eCRF. Special situations leading to an AE have to be recorded in the AE/SAE form in eCRF. AEs considered serious or related will be reported to PhV.

Definition of special situations:

- Breastfeeding - Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.
- Lack of therapeutic efficacy
- Overdose, abuse, off-label use, misuse, medication error or occupational exposure:
    - Abuse of a medicinal product - Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].
    - Medication error - refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.
    - Misuse of a medicinal product - Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. See also Misuse of a medicinal product for illegal purposes Misuse of a medicinal product for illegal purposes
    - Off-label use - Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information.
    - Overdose - Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information. Clinical judgment should always be applied.
    - Occupational exposure to a medicinal product - For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one’s professional or non-professional occupation.
- Unexpected benefits of drug

Information about special situations was collected following the Amendment#4, and only for patients who still did not complete End of Study visit at that time point.

5.6.11. Completing AE/SAE form in the eCRF

Summarized instructions on when to complete AE/SAE form in the eCRF are given in Table 6.

Table 6 Instruction when to complete the AE/SAE form in the eCRF

	Should AE/SAE form be completed ?
All AE (except from exempt AEs*)	Yes
Exempt AE*	**Only if** more severe and/or more important, or/and occurence is more frequent than it would be expected
Neutropenia and Febrile neutropenia	**Only if** there is suspicion of lack of efficacy due to immunogenicity/anti-drug-antibody reaction; or **if** more severe and/or more important, or/and occurence is more ferquent than it would be expected
Disease progression	Yes
Death due to disease progression	Yes
Special situations	**Only if** special situation led to an AE

*Nausea and vomiting, alopecia, diarrhoea and constipation, fatigue, asthenia, (neuropathic) pain, hand-foot-syndrome, swelling, mouth sores, appetite changes, nervous system effects only if related to chemotherapy treatment, cognitive changes or dysfunction only if related to chemotherapy treatment.

All AEs recorded in AE/SAE form in eCRF were to be reported to PhV if considered serious or related.

5.7. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, case report form and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy were achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in CRO’s Standard Operating Procedures (SOPs).

No study specific audits were performed for this study.

5.8. Statistical methods

5.8.1. Primary endpoints

The primary endpoints were:

- The mean number of days of delay of CT for each cycle
- The proportion of patients with CT doses reduced, omitted or delayed for each CT cycle

5.8.2. Secondary endpoints

The secondary endpoints were:

- Omission of BT
- Dose reduction of BT
- The baseline characteristics of patients receiving Lonquex®
- The incidence of FN in the first cycle and the incidence of FN in subsequent cycles
- The incidence of neutropenia (total and according to grade) in different cycles
- The number of days in hospital in different cycles for any reason, for reason of FN, or for reason of CIN
- The number of days in intensive care unit in different cycles
- The use of anti-infectives and anti-mycotics based on the number of days of treatment in different cycles
- The incidence of treatment with intravenous antibiotics due to FN or connected infections
- The incidence of AEs
- The incidence of ADRs
- The incidence of SAEs and SADRs
- The number of blood transfusions
- The mortality
- The evolution of the quality of life, in terms of EORTC QLQ-C30 and Brief Pain Inventory (BPI) scores
- The analysis of study population:
  - The proportion of patients with absolute or overall FN risk >20% receiving Lonquex®
  - The proportion of patients with FN risk 10-20% receiving Lonquex®
  - The proportion of patients with FN risk < 20% receiving Lonquex®

5.8.3. Determination of sample size

A total of approximately 1300 patients had to be included in the study. The sample size was not the result of a formal sample size calculation, but was instead the conclusion of feasibility considerations in all countries participating in the study.

5.8.4. Study cohorts /data sets analysed

- The full analysis set (FAS) included all enrolled patients who satisfy the eligibility criteria.
- The safety set included all patients having received Lonquex at least once.
- The efficacy set included all patients from the safety set for whom at least one cycle with Lonquex had post-baseline efficacy evaluation.

5.8.5. Derived and transformed data

In accordance with the Statistical Analysis Plan (SAP – Amendment 3 – dated 27 June 2017), the following data were derived:

- Cancer duration (year) = (Baseline visit date – Date of first diagnosis of malignant tumour) / (60 x 60 x 24 x 365.25)
- Time since start of Lonquex® in secondary prophylaxis for FN (day) = (Baseline visit date – Start date of treatment in secondary prophylaxis for FN) / (60 x 60 x 24)
- Time since start of Lonquex® in secondary prophylaxis for CIN (day) = (Baseline visit date – Start date of treatment in secondary prophylaxis for CIN) / (60 x 60 x 24)
- EORTC Physical Functioning = MEAN(questions 1 to 5)
- EORTC Role Functioning = MEAN(questions 6 and 7)
- EORTC Dyspnoea = question 8
- EORTC Pain = MEAN(questions 9 and 19)
- EORTC Fatigue = MEAN(questions 10, 12 and 18)
- EORTC Sleep = question 11
- EORTC Appetite = question 13
- EORTC Nausea/Vomiting = MEAN(questions 14 and 15)
- EORTC Constipation = question 16
- EORTC Diarrhoea = question 17
- EORTC Cognitive Functioning = MEAN(questions 20 and 25)
- EORTC Emotional Functioning = MEAN(questions 21 to 24)
- EORTC Social Functioning = MEAN(questions 26 and 27)
- EORTC Financial Difficulties = question 28
- EORTC Overall Health = question 29
- EORTC Overall QoL = question 30
- BPI: Pain Severity Score = MEAN(Questions 3 to 6)

- BPI: Pain Interference Score = MEAN(Questions 9 a to g)
- Anti-infective treatment duration (day) = (End date of anti-infective – Start date of anti-infective) / (60 x 60 x 24)
- Anti-mycotic treatment duration (day) = (End date of anti-mycotic – Start date of anti-mycotic) / (60 x 60 x 24)
- Study duration (day) = (Date of conclusion – Baseline visit) / (60 x 60 x 24)

5.8.6. Analysis of demographics

Descriptive statistics were used to characterize the population at baseline:

- Continuous variables were characterised by the N, n with missing data, mean, standard deviation (SD), median, minimum and maximum.
- Discrete variables were characterised by the N, n for each category, n with missing data and corresponding percentages.

5.8.7. Analysis of study endpoints

All endpoints were analysed using descriptive statistics.

No formal statistical hypotheses testing were conducted.

AEs, SAEs, ADRs and SADRs were coded with the Medical Dictionary for Regulatory Affairs (MedDRA; Version 20.0) and were summarized by System Organ Class (SOC) and Preferred Term (PT).

5.8.8. Interim analysis

An Interim Clinical Study Report (dated 19 January 2017) at the European level has been written on the basis of the data collected until 14 March 2016, in 622 patients from 7 countries.

The same analyses were repeated in lymphoma patients and a Statistical Report was issued in this specific population on 10 January 2017.

5.9. Changes in the conduct of the study or planned analyses

5.9.1. Protocol amendments

There were four amendments to the Study protocol template dated 1 August 2014.

- Amendment 1 and 2 dated 25 November 2014
- Amendment 3 dated 11 February 2015
- Amendment 4 dated 1 December 2015

In summary, the following changes have been introduced through these amendments:

- Synopsis has been aligned with the core text of the study protocol
- Good Clinical Practice (GCP) has been added among the references guiding the study.
- The patient identification number assignment has been corrected as follows: 2 letters for the country code, followed by 5 digits (2 for the centre and 3 for the patient), separated by hyphens.
- The primary objective has been rephrased to emphasize the fact that routine clinical practice is applicable
- The procedure of collection of signed informed consent has been detailed: Informed consent has to be obtained before any data collection and data procedures, including CT administration in the first chemotherapy cycle within this study.
- It has been clarified that the FN risk will be assessed by the investigator on the basis of received CT and patient's characteristics.
- Wording for some secondary variables has been corrected
- Some study procedures and assessments for each visit have been either deleted or added; or additional clarifications have been provided to align with the standard clinical practice
- Table 1 with study procedures and assessments has been adapted to be in agreement with the study procedures described in the next section of the protocol.
- Safety part has been adjusted to better define:
    - Which AEs have to be recorded in the AE/SAE section of eCRF
    - Which AEs are exempted from reporting
    - Which AEs are not reported expediently
    - When neutropenia and FN have to be reported as AE/SAE
    - That disease progression should be recorded in AE/SAE form in eCRF
- The different categories for qualifying the relationship between an AE and the drug have been specified: Probable - Possible - Unlikely - Not assessable - Not related. Categories Probable - Possible - Unlikely - Not assessable will be considered as reasonable possibility.
- All SAEs and non-serious ADRs must be reported within 24 hours of when the physician learns about it. The postponement for weekend or national holiday has been deleted.
- Special situations and requirements for reporting of special situations have been defined

5.9.2. Other changes

The reference document for this statistical analysis is the Statistical Analysis Plan (SAP – amendment 3 - dated 27 June 2017).

There were no changes to the planned analyses in the 3rd amendment of the SAP.

The efficacy population being almost the same as the safety population both in terms of number of patients (99.4% similarity) and number of cycles (99.7% similarity), the demographics, baseline characteristics and comorbidities analyses have been reported in the safety population only. The results obtained in the efficacy population are available as an annex to this report in an Acrobat Reader format (PDF).

6. STUDY POPULATION RESULTS

6.1. Number of patients and attrition from the study

A total of 1,339 patients were enrolled into the studies by 9 European countries (Austria, Belgium, Czech Republic, Italy, Luxembourg, Poland, Slovakia, Spain, The Netherlands) (Figure 1).

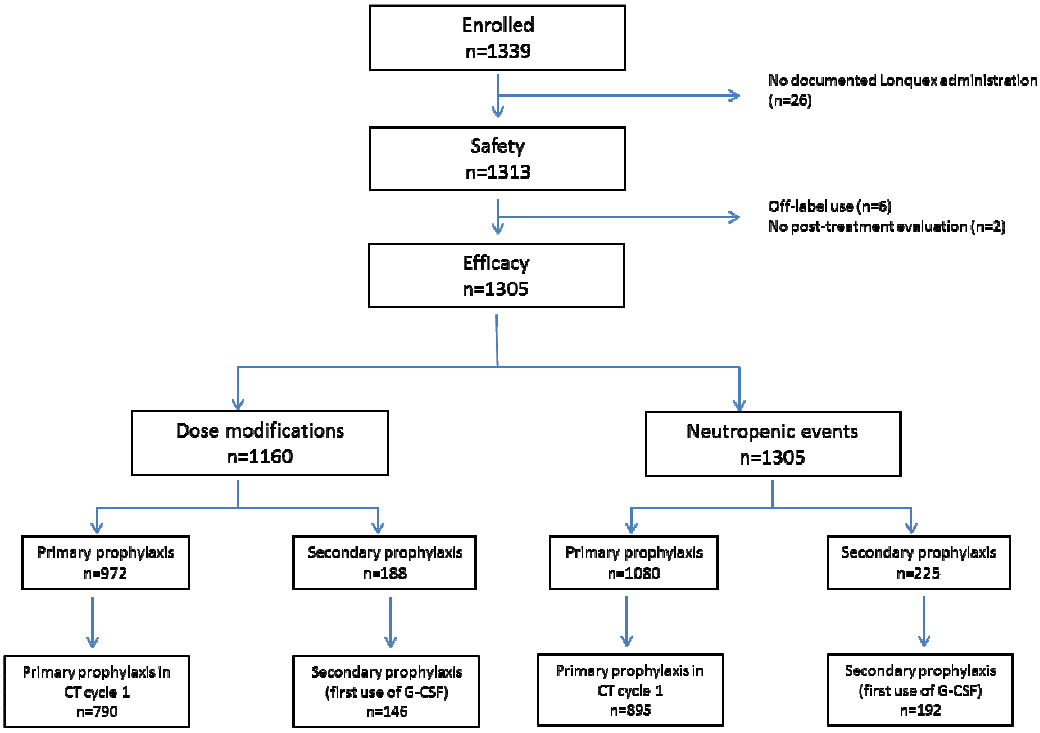
Twenty-six (N=26) patients were eliminated because they did not receive Lonquex. These patients were the following: AT-05-031, AT-05-040, BE-17-001, CZ-07-001, ES-03-003, ES-03-004, ITL-01-022, ITL-01-024, ITL-06-004, ITL-06-016, ITL-06-017, ITL-08-010, ITL-12-013, ITL-15-003, ITL-15-008, ITL-22-005, ITL-23-003, ITP-14-001, ITP-19-011, NL-08-001, NL-08-013, PL-02-003, SK-003-002, SK-003-003, SK-016-004 and SK-018-001.

A total of 1,313 patients were included in the safety population.

Eight (N=8) patients (CZ-02-010, ITP-01-003, ITP-07-002, ITP-07-003, ITP-07-004, ITP-07-005, ITP-07-006 and ITP-21-012) were eliminated from the efficacy analyses, either because they had no evaluation after Lonquex administration (N=1) or for another reason (N=7). Five of these 7 patients were eliminated because they had a conditioning regimen for ASCT, the 6th patient had a stem cell mobilization and the 7th patient went to another oncology department, and withdrew from the study. The efficacy population therefore included a total of 1,305 patients.

The incidence of neutropenic events could be evaluated in 1305 patients, whereas dose medications were evaluable in 1160 patients. The reason for this is that within this study Lonquex was administered in one CT cycle only for 145 patients.

Figure 1 STROBE diagram: number of patients and attrition from the study



A total of 885 (67.4%) patients completed the study, 424 (32.3%) patients discontinued (i.e., did not receive Lonquex in all CT cycles) the study and cycles were ongoing in 4 patients (0.3%) (Table 8).

A conclusion visit was available for 1,309 patients (99.7%). Conclusion visit dates ran from 13 January 2015 to 07 December 2017. Among the 1,309 patients with a conclusion, 885 (67.6%) patients received Lonquex at each of their CT cycles and 424 patients (32.4%) did not.

At this conclusion visit, among the patients who did not receive Lonquex at each cycle, the reasons for not receiving it during all CT cycles were:

- a lack of efficacy (N=2; 0.5%),
- a decision of patient to withdraw (N=25; 5.9%),
- a decision of the physician (N=103; 24.3%),
- an adverse event (N=34; 8.0%) or
- another reason (N=259; 61.2%).
- The information was missing for one patient (0.2%).

The other reasons are summarized in Table 9.

The characterization of the safety and efficacy populations can be seen in Table 7.

Table 7 Characterization of the safety and efficacy populations

	Safety population	Efficacy population
Patients with at least one cycle (n)	1,313	1,305
Number of cycles (treatment cycles and end of study visit)	7,234	7,215
Average number of cycles per patient	5.51	5.53
Patients with at least one treatment cycle (n)	1,313	1,305
Number of treatment cycles with Lonquex	5,607	5,597
Average number of treatment cycles with Lonquex per patient	4.27	4.29

In the safety population, the mean total study duration (end of study visit – baseline visit) was 4.26 ± 2.00 months, and the mean total time between the last cycle with Lonquex and the end of study visit was 1.73 ± 1.16 months.

In the efficacy population, the mean total study duration (end of study visit – baseline visit) was 4.28 ± 2.00 months and the mean total time between the last cycle with Lonquex and the end of study visit was 1.73 ± 1.17 months.

Table 8 Status of the patients (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Study completed	*885*	*67.4*	*67.4*	*67.4*
	Discontinued	*424*	*32.3*	*32.3*	*99.7*
	Ongoing cycle	*4*	*.3*	*.3*	*100.0*
	Total	*1313*	*100.0*	*100.0*	

Table 9 Other reasons for not receiving Lonquex during all CT cycles (Safety population)

		Frequency	Percent
Valid	Lonquex received at each cycle	885	67.6
	Missing information	1	0.1
	Lack of efficacy, decision of the patient, decision of the investigator or AE	164	12.5
	Administration mistake	2	.2
	Administrative mistake	1	.1
	AE	4	.3
	AE and FN prophylaxis not needed during weekly CT regimen	1	.1
	Another G-CSF administered	13	1.0
	CT discontinued	14	1.1
	CT regimen changed	10	.8
	Death	1	.1
	Decision of patient	1	.1
	Decision of patient to withdraw	1	.1
	Decision of the patient and physician	1	.1
	Disease progression	6	.5
	Enrollment in the study at later cycle	31	2.4
	FN prophylaxis initiated at later cycle	7	.5
	FN prophylaxis not needed during trastuzumab monotherapy	1	.1
	FN prophylaxis not needed during weekly CT regimen	64	4.9
	FN prophylaxis not needed during weekly CT regimen and during trastuzumab treatment	2	.2
	Lonquex not available	1	.1
	Lost to follow up	11	.8
	Low risk of FN	1	.1
	No Lonquex in weekly part of CT regimen	4	.3
	No more risk of neutropenia	1	.1
	Other G-CSF administered	2	.2
	Patient did not come to the planned visit	1	.1
	Patient to proceed to HSCT	1	.1
	Patient to proceed to PBSC harvesting	6	.5
	Price of the drug	1	.1
	Risk increased at later cycles	1	.1
	Secondary prophylaxis	5	.4
	Unknown	64	4.9
	Total	1309	100.0

6.2. Demographics and baseline characteristics of the patients

Patients (N=1,313; safety population) were 58.4 ± 13.3 years-old on average, with a median of 59 years, a minimum of 19 years and a maximum of 95 years (Table 10).

From diagnosis till inclusion in this study, their cancer had lasted for a mean of 1.12 ± 2.85 years, with a median of 0.17 year, a minimum of 0 year and a maximum of 36.08 years (40 missing values) (Table 10).

There were 391 males (29.8%) and 922 females (70.2%).

The ethnicity was as follows: 1,155 Caucasians (88.0%), 2 Blacks (0.2%), 8 Asians (0.6%) and 5 Hispanics (0.4%) (139 missing values).

Table 10 Demographics and baseline characteristics (Safety population)

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
Age (year)	***1313***	***0***	***58.38***	***59.00***	***13.280***	***19***	***95***
Planned CT cycle duration (week)	***1291***	***22***	***4.35***	***3.00***	***6.103***	***0***	***84***
Planned CT number of cycles	***1286***	***27***	***6.57***	***6.00***	***3.492***	***1***	***21***
CT cycle duration till start of secondary prophylaxis (week)	***221***	***0***	***3.76***	***3.00***	***3.232***	***1***	***24***
CT number of cycles till start of secondary prophylaxis	***221***	***0***	***2.74***	***2.00***	***2.765***	***0***	***20***
Cancer duration (year)	***1273***	***40***	***1.1184***	***.1725***	***2.85153***	***.00***	***36.08***
Time since FN as reported at baseline till start of Lonquex in secondary prophylaxis (day)	***48***	***0***	***20.6042***	***13.0000***	***22.49231***	***.00***	***102.00***
Time since CIN as reported at baseline till start of Lonquex in since prophylaxis (day)	***207***	***0***	***24.3478***	***11.0000***	***62.58660***	***.00***	***746.00***
Number of risk factors	***1313***	***0***	***2.0160***	***2.0000***	***1.23178***	***.00***	***8.00***

The primary tumors are detailed in Table 11. The most frequent cancer affected the breast (46.7%), the lymphatic system (lymphoma; 26.4%), the lung (4.1%), the ovary (3.4%) and the prostate (3.0%).

Table 11 Primary tumor (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Bladder	8	.6	.6	.6
	Blood	27	2.1	2.1	2.7
	Bone	1	.1	.1	2.7
	Breast	613	46.7	46.7	49.4
	Brain	1	.1	.1	49.5
	Cervix	3	.2	.2	49.7
	Colon	25	1.9	1.9	51.6
	Duodenum	1	.1	.1	51.7
	Endometrium	15	1.1	1.1	52.9
	Gallbladder	3	.2	.2	53.1
	Germ cells	3	.2	.2	53.3
	Head	8	.6	.6	53.9
	Larynx	3	.2	.2	54.2
	Lung	54	4.1	4.1	58.3
	Lymphoma	347	26.4	26.4	84.7
	Neck	3	.2	.2	84.9
	Ovary	44	3.4	3.4	88.3
	Pancreas	19	1.4	1.4	89.7
	Prostate	40	3.0	3.0	92.8
	Rectum	4	.3	.3	93.1
	Salivary glands	3	.2	.2	93.3
	Skin	1	.1	.1	93.4
	Stomach	16	1.2	1.2	94.6
	Testicle	17	1.3	1.3	95.9
	Neuroendocrine	3	.2	.2	96.1
	Vulva	1	.1	.1	96.2
	Soft tissue sarcoma	2	.2	.2	96.3
	Squamous cell cancer of the extremity	1	.1	.1	96.4
	Multiple myeloma	15	1.1	1.1	97.6
	Melanoma	1	.1	.1	97.6
	Uterus	4	.3	.3	97.9
	Ileum	2	.2	.2	98.1
	Thymus	2	.2	.2	98.2
	Oral cavity	4	.3	.3	98.6
	Ewing sarcoma	1	.1	.1	98.6
	Ethmoid sarcoma	1	.1	.1	98.7
	Sclerosing epithelioid fibrosarcoma	1	.1	.1	98.8

		Frequency	Percent	Valid Percent	Cumulative Percent
	Uterus. peritoneum. ear	***1***	***.1***	***.1***	***98.9***
	Oropharynx	***1***	***.1***	***.1***	***98.9***
	Esophagogastric junction	***1***	***.1***	***.1***	***99.0***
	Leiomyosarcoma	***1***	***.1***	***.1***	***99.1***
	Neuroendocrine lung	***1***	***.1***	***.1***	***99.2***
	Soft tissue sarcoma extremity	***3***	***.2***	***.2***	***99.4***
	Myoepithelial	***1***	***.1***	***.1***	***99.5***
	Hairy cell leukemia	***2***	***.2***	***.2***	***99.6***
	Chronic lymphocytic leukemia	***3***	***.2***	***.2***	***99.8***
	Trachea	***1***	***.1***	***.1***	***99.9***
	Unknown	***1***	***.1***	***.1***	***100.0***
	Total	***1313***	***100.0***	***100.0***	

Individual risk factors for febrile neutropenia (FN) were present in 1,249 (95.1%) patients. They consisted of advanced disease in 378 (28.8%) patients, an age above 65 years for 487 (37.1%) patients, an history of prior FN for 117 (8.9%) patients, a poor performance status for 52 (4.0%) patients, a poor nutritional status for 61 (4.6%) patients, a female gender for 922 (70.2%) patients, an hemoglobin level <12 g/dL for 278 (21.2%) patients, a liver disease for 44 (3.4%) patients, a renal disease for 28 (2.1%) patients, a cardiovascular disease for 201 (15.3%) patients and another condition for 79 (6.0%) patients.

Overall, the mean number of risk factors was 2.02 ± 1.23 (Table 10).

The **tumour size** was T0 for 2 (0.2%) patients, T1 for 219 (16.7%) patients, T2 for 305 (23.2%) patients, T3 for 151 (11.5%) patients, T4 for 88 (6.7%) patients and Tx for 83 (6.3%) patients. The information was not applicable for 447 (34.0%) patients and missing for 18 (1.4%) patients.

Lymph nodes were N0 for 279 (21.2%) patients, N1 for 255 (19.4%) patients, N2 for 118 (9.0%), N3 for 57 (4.3%) and Nx for 139 (10.6%) patients. The information was not applicable for 447 (34.0%) patients and missing for 18 (1.4%) patients.

Metastasis was M0 for 536 (40.8%) patients, M1 for 185 (14.1%) patients and Mx for 126 (9.6%) patients. The information was not applicable for 447 (34.0%) patients and missing for 19 (1.4%) patients.

The **ECOG performance status** was available for 1,296 patients. It was equal to:
- 0 for 847 (64.5%) patients,
- 1 for 376 (28.6%) patients,
- 2 for 53 (4.0%) patients,
- 3 for 18 (1.4%) patients and
- 4 for 2 (0.2%) patients.

History of FN without antibiotic prophylaxis nor G-CSF prophylaxis was found in 93 (7.1%) patients. The information was missing for 18 (1.4%) patients.

A **nutritional deficiency** was found in 59 (4.5%) patients. The information was missing for 19 patients (1.4%)..

Previous treatments of cancer consisted of:
- surgery in 548 (41.7%) patients,
- chemotherapy in 374 (28.5%) patients,
- radiotherapy in 158 (12.0%) patients
- hormonal treatment in 83 (6.3%) patients and/or
- another treatment in 43 (3.3%) patients.
- No previous cancer treatment had been provided to 480 (36.6%) patients.
- The information was missing for 17 (1.3%) patients.

Chemotherapy (CT) was planned for 1,312 (99.9%) patients. No CT was planned for one patient (CZ-03-005).

The planned CT regimen can be found in Table 12 and the other planned CT regimen can be found in Table 13.

Table 12 Planned CT regimen (Safety population)

		Frequency	Percent
Valid	Paclitaxel/carboplatin	11	.8
	DDGc MVAC	1	.1
	TPF	2	.2
	AC --> docetaxel	26	2.0
	Docetaxel --> AC	2	.2
	Doxorubicin/docetaxel	12	.9
	TAC	48	3.7
	DD/DDG FEC	3	.2
	DDGc doxorubicin/cyclophosphamide --> paclitaxel	10	.8
	DDG epirubicin/cyclophosphamide	8	.6
	AC	7	.5
	Docetaxel	13	1.0
	FEC-D	18	1.4
	FEC-100	9	.7
	AC	3	.2
	Epidoxorubicin/cyclophosphamide	15	1.1
	FEC 120	1	.1

	CMF	***3***	***.2***
	Doxorubicin/cyclophosphamide	***25***	***1.9***
	Doxorubicin/cyclophosphamide --> paclitaxel	***24***	***1.8***
	FAC 50	***11***	***.8***
	Epirubicin/cyclophosphamide +/- lonidamide	***2***	***.2***
	FEC	***20***	***1.5***
	Epirubicin/cyclophosphamide	***30***	***2.3***
	Epirubicin/paclitaxel or epirubicin --> paclitaxel --> CMF	***1***	***.1***
	Docetaxel --> epirubicin --> DEC	***2***	***.2***
	Epirubicin/cyclophosphamide with withdrawal of 5-FU	***3***	***.2***
	Paclitaxel/cisplatin	***1***	***.1***
	FOLFIRI	***5***	***.4***
	FOLFOX	***13***	***1.0***
	Cisplatin/etoposide	***8***	***.6***
	BEP --> EP	***1***	***.1***
	Etoposide/carboplatin	***15***	***1.1***
	Topotecan/cisplatin	***1***	***.1***
	Docetaxel/carboplatin	***2***	***.2***
	Etoposide/cisplatin	***8***	***.6***
	Docetaxel/cisplatin	***2***	***.2***
	Gemcitabine/cisplatin	***1***	***.1***
	Bevacizumab/paclitaxel/carboplatin	***2***	***.2***
	Docetaxel	***14***	***1.1***
	Paclitaxel/carboplatin	***17***	***1.3***
	Gemcitabine/cisplatin	***1***	***.1***
	FOLFIRI	***2***	***.2***
	LVFU	***1***	***.1***
	LVFU-cisplatin	***3***	***.2***
	LVFU-irinotecan	***1***	***.1***
	DCF	***1***	***.1***
	ECF	***3***	***.2***
	FOLFOX-6	***2***	***.2***
	DHAP	***6***	***.5***
	CHOP-21	***23***	***1.8***
	CHOP-14	***5***	***.4***
	R-CHOP	***34***	***2.6***
	BEACOPP	***1***	***.1***
	ICE	***4***	***.3***
	R-ICE	***1***	***.1***

	R-CHOP	***49***	***3.7***
	MAID	***2***	***.2***
	Doxorubicin/cisplatin	***1***	***.1***
	Other	***772***	***58.8***
	Total	***1312***	***99.9***
Missing	**System**	***1***	***.1***
Total		***1313***	***100.0***

Table 13 Other planned CT regimen (Safety population)

		Frequency	**Percent**
Valid	**ABVD**	***19***	***1.4***
	AVD	***3***	***.2***
	B-GEV (bendamustine/gemcitabine/vinorelbine)	***1***	***.1***
	Bendamustine	***10***	***.8***
	Bendamustine/cytarbine	***1***	***.1***
	Bendamustine/gemcitabine/dexamethasone	***1***	***.1***
	Bleomycin/doxorubicin/vincristine/dexamethasone	***1***	***.1***
	Bleomycin/etoposide/cisplatin (BEP)	***15***	***1.1***
	BMR	***1***	***.1***
	Bortezomib/cyclophosphamide/dexamethasone (VCD)	***1***	***.1***
	Brentuximab vedotin	***1***	***.1***
	Cabazitaxel	***15***	***1.1***
	Cabazitaxel/prednisolone	***1***	***.1***
	CAPOX	***1***	***.1***
	Carboplatin	***4***	***.3***
	Carboplatin/5-FU/cetuximab	***1***	***.1***
	Carboplatin/docetaxel	***7***	***.5***
	Carboplatin/docetaxel/5-FU	***2***	***.2***
	Carboplatin/doxorubicin	***3***	***.2***
	Carboplatin/epirubicin	***1***	***.1***
	Carboplatin/etoposide	***3***	***.2***
	Carboplatin/gemcitabine	***3***	***.2***
	Carboplatin/gemcitabine/bevacizumab	***1***	***.1***
	Carboplatin/paclitaxel	***10***	***.8***
	Carboplatin/paclitaxel -> DD epirubicin/cyclophosphamide	***11***	***.8***
	Carboplatin/paclitaxel -> epirubicin/cyclophosphamide	***2***	***.2***
	Carboplatin/pemetrexed	***1***	***.1***
	Carboplatin/vinorelbin	***2***	***.2***

	Chlorambucil	***2***	***.2***
	CHOEP	***12***	***.9***
	Cisplatin	***1***	***.1***
	Cisplatin/5-FU	***2***	***.2***
	Cisplatin/5-FU/cetuximab	***2***	***.2***
	Cisplatin/cyclophosphamide	***1***	***.1***
	Cisplatin/docetaxel/5-FU	***4***	***.3***
	Cisplatin/docetaxel/5-FU -> cisplatin	***1***	***.1***
	Cisplatin/docetaxel/5-FU -> cisplatin/RT	***1***	***.1***
	Cisplatin/doxorubicin/cyclophosphamide	***2***	***.2***
	Cisplatin/doxorubicin/etoposide	***1***	***.1***
	Cisplatin/epirubicin	***1***	***.1***
	Cisplatin/etoposide	***6***	***.5***
	Cisplatin/etoposide/bleomycine (PEB)	***3***	***.2***
	Cisplatin/gemcitabin	***1***	***.1***
	Cisplatin/gemcitabine	***2***	***.2***
	Cisplatin/paclitaxel	***1***	***.1***
	Cisplatin/pemetrexed	***9***	***.7***
	Cisplatin/raltitrexed	***1***	***.1***
	Cladribine	***3***	***.2***
	COMP	***6***	***.5***
	COP	***1***	***.1***
	CTD	***1***	***.1***
	CVP/R-CVP	***3***	***.2***
	Cyclophosphamide	***14***	***1.1***
	Cyclophosphamide -> paclitaxel	***2***	***.2***
	Cyclophosphamide/dexamethasone	***1***	***.1***
	Cyclophosphamide/doxorubicin/cisplatin	***1***	***.1***
	Cyclophosphamide/liposomal doxorubicin/5-FU	***1***	***.1***
	Cyclophosphamide/methotrexate/5-FU	***1***	***.1***
	Cyclphosphamid/docetaxel	***1***	***.1***
	D-PACE	***1***	***.1***
	DA-EPOCH	***8***	***.6***
	DA-EPOCH-R	***1***	***.1***
	Dacarbazine/epirubicin	***1***	***.1***
	Daratumumab/bortezomib/dexamethason	***1***	***.1***
	DD doxorubicin/cyclophosphamide -> carboplatin/paclitaxel	***1***	***.1***
	DD doxorubicin/cyclophosphamide -> paclitaxel	***1***	***.1***
	DD Epirubicin/cyclophosphamide	***1***	***.1***

	DD Epirubicin/cyclophosphamide -> carboplatin/paclitaxel	***1***	***.1***
	DD Epirubicin/cyclophosphamide -> docetaxel	***1***	***.1***
	DD Epirubicin/cyclophosphamide -> paclitaxel	***30***	***2.3***
	DD Epirubicin/cyclophosphamide -> paclitaxel/bevacizumab	***1***	***.1***
	DD Epirubicin/cyclophosphamide -> paclitaxel/trastuzumab	***5***	***.4***
	DD Methotrexate/vinblastine/doxorubicin/cisplatin (MVAC)	***1***	***.1***
	Dexamethasone/cytarabine/carboplatin	***1***	***.1***
	Docetaxel	***15***	***1.1***
	Docetaxel -> FEC	***1***	***.1***
	Docetaxel -> paclitaxel	***1***	***.1***
	Docetaxel/5-FU	***1***	***.1***
	Docetaxel/carboplatin/trastuzumab	***1***	***.1***
	Docetaxel/cisplatin	***2***	***.2***
	Docetaxel/cyclophosphamide	***23***	***1.8***
	Docetaxel/cyclophosphamide -> trastuzumab	***1***	***.1***
	Docetaxel/cyclophosphamide/trastuzumab	***1***	***.1***
	Docetaxel/prednisolone	***5***	***.4***
	Docetaxel/prednisone	***2***	***.2***
	Docetaxel/trastuzumab/pertuzumab	***8***	***.6***
	Doxorubicin	***1***	***.1***
	Doxorubicin/cyclophosphamide	***5***	***.4***
	Doxorubicin/cyclophosphamide -> docetaxel	***2***	***.2***
	Doxorubicin/cyclophosphamide -> paclitaxel	***3***	***.2***
	Doxorubicin/cyclophosphamide -> paclitaxel/trastuzumab	***1***	***.1***
	Doxorubicin/cyclophosphamide/vincristine (ACO)	***2***	***.2***
	Doxorubicin/docetaxel/cyclophosphamide	***2***	***.2***
	Doxorubicin/ifosfamide	***2***	***.2***
	Doxorubicin/ifosfamide/mesna	***2***	***.2***
	Doxorubicin/paclitaxel	***1***	***.1***
	eBEACOPP	***1***	***.1***
	Epirubicin	***1***	***.1***
	Epirubicin/cyclophoshamide -> docetaxel	***1***	***.1***
	Epirubicin/cyclophosphamide	***1***	***.1***
	Epirubicin/cyclophosphamide --> Paclitaxel	***1***	***.1***
	Epirubicin/cyclophosphamide -> docetaxel	***11***	***.8***
	Epirubicin/cyclophosphamide -> docetaxel/carboplatin	***6***	***.5***
	Epirubicin/cyclophosphamide -> docetaxel/trastuzumab	***2***	***.2***
	Epirubicin/cyclophosphamide -> paclitaxel	***45***	***3.4***
	Epirubicin/cyclophosphamide -> paclitaxel/trastuzumab	***5***	***.4***

	Epirubicin/cyclophosphamide/docetaxel	***1***	***.1***
	Epirubicin/cyclophosphamide/paclitaxel	***1***	***.1***
	Epirubicin/docetaxel	***6***	***.5***
	Epirubicin/ifosfamide	***3***	***.2***
	Epirubicin/ifosfamide/mesna	***1***	***.1***
	Epirubicin/paclitaxel	***1***	***.1***
	Epirubicine/cyclophosphamide/paclitaxel	***1***	***.1***
	Eribulin	***1***	***.1***
	Etoposide/oxaliplatin/capecitabine	***1***	***.1***
	F-CR	***1***	***.1***
	FAC	***1***	***.1***
	FAC -> docetaxel/trastuzumab	***1***	***.1***
	FC	***1***	***.1***
	FC-R	***17***	***1.3***
	FEAM	***3***	***.2***
	FEC	***4***	***.3***
	FEC - > radiation -> docetaxel	***3***	***.2***
	FEC -> docetaxel	***70***	***5.3***
	FEC -> docetaxel - > FEC	***1***	***.1***
	FEC -> docetaxel/trastuzumab	***2***	***.2***
	FEC -> paclitaxel	***4***	***.3***
	FEC -> paclitaxel/trastuzumab	***1***	***.1***
	FLOX-LF	***1***	***.1***
	FOLFIRI	***1***	***.1***
	FOLFIRINOX	***12***	***.9***
	FOLFOXIRI	***2***	***.2***
	Gemcitabine	***4***	***.3***
	Gemcitabine/docetaxel	***1***	***.1***
	Gemcitabine/paclitaxel protein-bound	***1***	***.1***
	GEMOX	***2***	***.2***
	High-dose cyclophosphamide	***2***	***.2***
	High-dose cytarbine	***1***	***.1***
	Ifosfamide	***2***	***.2***
	Ifosfamide/carboplatin	***1***	***.1***
	ifosfamide/vincristine/actinomycin D/doxorubicin (IVADo)	***1***	***.1***
	IGEV	***7***	***.5***
	IGEV/DHAP	***1***	***.1***
	Irinotecan	***1***	***.1***
	Irinotecan/5-FU	***1***	***.1***

	Irinotecan/oxaliplatin/5-fluorouracil	***1***	***.1***
	IROX	***1***	***.1***
	Lenalidomide/cyclophosphamide/prednisone (REP)	***1***	***.1***
	Lenalidomide/dexamethason	***3***	***.2***
	Liposomal doxorubicin	***2***	***.2***
	Liposomal doxorubicin/cyclophosphamide/docetaxel	***1***	***.1***
	MBVD (Myocet + BVD)	***4***	***.3***
	megaCEOP 14	***1***	***.1***
	Melphalan	***2***	***.2***
	Methotrexate -> R-CHOP	***1***	***.1***
	Methotrexate/cytarabine/cyclophosphamide	***1***	***.1***
	miniDHAP	***1***	***.1***
	Mitoxantrone	***1***	***.1***
	MVD (Myocet/vinblastine/dacarbazine)	***1***	***.1***
	Non-pegylated liposomal doxorubicin/cyclophosphamide	***2***	***.2***
	Non-pegylated liposomal doxorubicin/cyclophosphamide/docetaxel	***1***	***.1***
	Obinutuzumab/chlorambucil	***2***	***.2***
	Oxaliplatin	***1***	***.1***
	Oxaliplatin/levofolinic acid	***1***	***.1***
	Paclitaxel	***2***	***.2***
	Paclitaxel -> DD epirubicin/cyclophosphamide	***3***	***.2***
	Paclitaxel protein-bound	***4***	***.3***
	Paclitaxel protein-bound/epirubicin/carboplatin/cyclophosphamide	***1***	***.1***
	Paclitaxel protein-bound/FEC	***1***	***.1***
	Paclitaxel/cyclophosphamide	***1***	***.1***
	Paclitaxel/trastuzumab -> epirubicin/cyclophosphamide	***1***	***.1***
	Paclitaxel/trastuzumab/carboplatin/pertuzumab	***1***	***.1***
	Palbociclib	***1***	***.1***
	Pegylated liposomal doxorubicin	***2***	***.2***
	Pegylated liposomal doxorubicin/cyclophosphamide	***1***	***.1***
	Pegylated liposomal doxorubicin/trabectadin	***1***	***.1***
	Pemetrexed	***1***	***.1***
	Pertuzumab/trastuzumab-FEC	***1***	***.1***
	Pertuzumab/trastuzumab-FEC -> pertuzumab/trastuzumab/docetaxel	***2***	***.2***
	Pomalidomide/prednison	***1***	***.1***
	R-BAC	***8***	***.6***
	R-BAC 500	***3***	***.2***
	R-bendamustin	***3***	***.2***
	R-bendamustine	***23***	***1.8***

	R-CEOP	***1***	***.1***
	R-chlorambucil	***1***	***.1***
	R-CHOP	***4***	***.3***
	R-CHOP 14	***3***	***.2***
	R-CHOP mini	***2***	***.2***
	R-CHOP/R-DHAOX	***2***	***.2***
	R-COMP	***39***	***3.0***
	R-COMP 14	***2***	***.2***
	R-COMP/R-cytarbine	***1***	***.1***
	R-COP	***2***	***.2***
	R-CVP	***7***	***.5***
	R-DAOX	***3***	***.2***
	R-dexamethasone	***1***	***.1***
	R-DHAOX	***1***	***.1***
	R-DHAP	***9***	***.7***
	R-DHAP/R-CHOP	***1***	***.1***
	R-GEMOX	***1***	***.1***
	R-GIFOX	***1***	***.1***
	R-IEV	***1***	***.1***
	R-megaCHOP	***1***	***.1***
	R-methotrexate/cytarabine	***1***	***.1***
	R-miniDHAP	***2***	***.2***
	RCD	***1***	***.1***
	Topotecan	***1***	***.1***
	Trabectedin	***3***	***.2***
	Vinblastine/ifosfamide/cisplatin (VeIP)	***1***	***.1***
	Vinflunine	***1***	***.1***
	VMP	***2***	***.2***
	XELOX	***1***	***.1***
	Total	***772***	***100.0***

The setting of CT was available in 1,290 patients (98.2%) and missing for 23 (1.8%) patients. It consisted of an adjuvant/induction setting in 731 (55.7%) patients, a neo-adjuvant/consolidation setting in 253 (19.3%) patients, a metastatic setting in 247 (18.8%) patients, a maintenance setting in 22 (1.7%) patients or another setting in 37 (2.8%) patients. The other settings are shown in Table 14.

The planned duration of CT cycles is 3 weeks in 792 (60.3%). It is 2 weeks in 198 (15.1%) patients, 4 weeks in 140 (10.7%) patients and 1 week in 35 (2.7%) patients. The planned number of CT cycles is 6 in 542 (41.3%) patients, 4 in 258 (19.6%) patients, 8 in 162 (12.3%) patients and 3 in 82 (6.2%) patients.

Table 14 Other settings use of CT (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No other CT setting	1281	97.6	97.6	97.6
	2nd line chemotherapy	3	.2	.2	97.8
	Advanced disease	3	.2	.2	98.0
	Conditioning regimen for ASCT	5	.4	.4	98.4
	Consolidation	1	.1	.1	98.5
	Curative	2	.2	.2	98.6
	Induction	1	.1	.1	98.7
	Locally advanced unresectable	1	.1	.1	98.8
	Palliative	1	.1	.1	98.9
	Re-induction	1	.1	.1	98.9
	Refractory disease	1	.1	.1	99.0
	Relapse	10	.8	.8	99.8
	Salvage chemotherapy	2	.2	.2	99.9
	Stem cell mobilization	1	.1	.1	100.0
	Total	1313	100.0	100.0	

The mean planned CT cycles duration was 4.35 ± 6.10 weeks (Table 10).

The mean number of CT cycles planned was 6.57 ± 3.49 (Table 10).

The setting of planned biological treatment (BT) was available for 376 (28.6%) patients. It consisted of an adjuvant/induction setting in 275 (20.9%) patients, a neo-adjuvant/consolidation setting in 41 (3.1%) patients, a metastatic setting in 37 (2.8%) patients, a maintenance setting in 11 (0.8%) patients or another setting in 12 (0.9%) patients. The list of BT can be found in Table 15.

Table 15 Planned biological treatments (Safety population)

		Frequency	Percent	Cumulative Percent
Valid	Trastuzumab	*73*	*19.4*	*19.4*
	Bevacizumab	*15*	*4.0*	*23.4*
	Cetuximab	*2*	*.5*	*23.9*
	Panitumumab	*1*	*.3*	*24.2*
	Irinotecan	*3*	*.8*	*25.0*
	Pemetrexed	*1*	*.3*	*25.3*
	Ramucirumab	*1*	*.3*	*25.5*
	Rituximab	*273*	*72.6*	*98.1*
	Other	*4*	*1.1*	*99.2*
	Pertuzumab	*3*	*.8*	*100.0*
	Total	*376*	*100.0*	

The overall FN risk was available in 1,296 (98.7%) patients and missing in 17 (1.3%) patients (15 patients from Slovakia and 2 patients from Italy). It was:

- low (<10%) for 127 (9.7%) patients,
- intermediate (10-20%) for 482 (36.7%) patients and
- high (>20%) for 687 (52.3%) patients.

In patients presenting an **intermediate FN risk** (10-20%) (N=482), individual risk factors for febrile neutropenia (FN) were present in 459 (95.2%) patients. They consisted of advanced disease in 142 (29.5%) patients, an age above 65 years for 195 (40.5%) patients, an history of prior FN for 50 (10.4%) patients, a poor performance status for 18 (3.7%) patients, a poor nutritional status for 24 (5.0%) patients, a female gender for 326 (67.6%) patients, an hemoglobin level <12 g/dL for 100 (20.7%) patients, a liver disease for 17 (3.5%) patients, a renal disease for 9 (1.9%) patients, a cardiovascular disease for 65 (13.5%) patients and/or another condition for 35 (7.3%) patients. Overall, the mean number of risk factors was 2.04 ± 1.23.

The type of prophylaxis use of Lonquex was available for all patients. The prophylaxis use was:

- primary for 1,088 (82.9%) patients and
- secondary for 225 (17.1%) patients.

The reason for starting Lonquex in secondary prophylaxis was available for those 223 patients. FN was evoked in 48 (21.5%) patients and chemotherapy-induced neutropenia (CIN) is evoked in 207 (93.2%) patients.

In case of secondary prophylaxis the use of CT at the time of FN and CIN was documented for 221 (99.1%) patients. The CT setting was also documented in 221 (99.1%) patients (Table 16 and Table 17). In those 221 patients, the setting of CT consisted of an adjuvant/induction setting in 128 (57.9%) patients, neo-

adjuvant/consolidation setting in 30 (13.6%) patients, metastatic setting in 49 (22.2%) patients, maintenance setting in 4 (1.8%) patients or another setting in 10 (4.5%) patients (consolidation for 1 patient, curative for 3 patients, relapse for 2 patients, palliative for 1 patient, locally advanced unresectable for 2 patients and post-surgery adjuvant after extirpation of local recurrent tumour).

Table 16 Chemotherapy regimen before starting Lonquex in SP (Safety population)

		Frequency	Percentage
Valid	Paclitaxel/carboplatin	3	1.4
	AC --> docetaxel	4	1.8
	Doxorubicin/docetaxel	1	.5
	TAC	1	.5
	DDGc doxorubicin/cyclophosphamide --> paclitaxel	5	2.3
	DDG epirubicin/cyclophosphamide	7	3.2
	AC	2	.9
	Docetaxel	6	2.7
	FEC-D	4	1.8
	FEC-100	4	1.8
	AC	2	.9
	Epidoxorubicin/cyclophosphamide	9	4.1
	CEF	2	.9
	CMF	1	.5
	Doxorubicin/cyclophosphamide --> paclitaxel	2	.9
	FAC 50	3	1.4
	FEC	5	2.3
	Epirubicin/cyclophosphamide	17	7.7
	Docetaxel --> epirubicin --> DEC	1	.5
	FOLFIRI	3	1.4
	FOLFOX	8	3.6
	Cisplatin/etoposide	3	1.4
	Etoposide/carboplatin	3	1.4
	Docetaxel/cisplatin	1	.5
	Gemcitabine/cisplatin	1	.5
	Docetaxel	2	.9
	Paclitaxel/carboplatin	2	.9
	FOLFIRI	2	.9
	LVFU-cisplatin	2	.9
	LVFU-irinotecan	1	.5
	ECF	1	.5

		Frequency	Percentage
	FOLFOX-6	***2***	***.9***
	DHAP	***1***	***.5***
	CHOP-21	***5***	***2.3***
	R-CHOP	***7***	***3.2***
	R-CHOP	***10***	***4.5***
	Other	***88***	***39.8***
	Total	***221***	***100.0***

Table 17 Other chemotherapy regimens before starting Lonquex in SP (Safety population)

		Frequency	Percent	Cumulative Percent
Valid	**ABVD**	***10***	***11.4***	***11.4***
	Bendamustine	***2***	***2.3***	***13.6***
	Bleomycin/etoposide/cisplatin (BEP)	***1***	***1.1***	***14.8***
	Carboplatin	***1***	***1.1***	***15.9***
	Carboplatin/docetaxel	***2***	***2.3***	***18.2***
	Carboplatin/gemcitabin/bevacizumab	***1***	***1.1***	***19.3***
	Carboplatin/paclitaxel	***3***	***3.4***	***22.7***
	Chlorambucil	***1***	***1.1***	***23.9***
	CHOEP	***2***	***2.3***	***26.1***
	Cisplatin/cyclophosphamide	***1***	***1.1***	***27.3***
	Cisplatin/etoposide	***1***	***1.1***	***28.4***
	Cisplatin/gemcitabin	***1***	***1.1***	***29.5***
	Cisplatin/gemcitabine	***1***	***1.1***	***30.7***
	Cladribine	***1***	***1.1***	***31.8***
	COMP	***1***	***1.1***	***33.0***
	COP	***1***	***1.1***	***34.1***
	CTD	***1***	***1.1***	***35.2***
	Cyclophosphamide	***1***	***1.1***	***36.4***
	Cyclophosphamide/doxorubicin/cisplatin	***1***	***1.1***	***37.5***
	Cyclophosphamide/methotrexate/5-FU	***1***	***1.1***	***38.6***
	Dacarbazine/epirubicin	***1***	***1.1***	***39.8***
	Docetaxel	***4***	***4.5***	***44.3***
	Docetaxel/cyclophosphamide	***2***	***2.3***	***46.6***
	Docetaxel/prednisolone	***1***	***1.1***	***47.7***
	Docetaxel/prednisone	***1***	***1.1***	***48.9***
	Docetaxel/trastuzumab/pertuzumab	***2***	***2.3***	***51.1***

	Doxorubicin/cyclophosphamide -> paclitaxel	***1***	***1.1***	***52.3***
	Epirubicin/cyclophosphamide	***2***	***2.3***	***54.5***
	Epirubicin/cyclophosphamide -> docetaxel	***1***	***1.1***	***55.7***
	Epirubicin/cyclophosphamide/docetaxel	***1***	***1.1***	***56.8***
	Epirubicin/paclitaxel	***1***	***1.1***	***58.0***
	Eribulin	***1***	***1.1***	***59.1***
	Etoposide/oxaliplatin/capecitabine	***1***	***1.1***	***60.2***
	FAC -> docetaxel/trastuzumab	***1***	***1.1***	***61.4***
	FC	***1***	***1.1***	***62.5***
	FC-R	***1***	***1.1***	***63.6***
	FEC	***1***	***1.1***	***64.8***
	FEC -> docetaxel	***2***	***2.3***	***67.0***
	FOLFIRINOX	***4***	***4.5***	***71.6***
	Gemcitabine/paclitaxel protein-bound	***1***	***1.1***	***72.7***
	High-dose cytarbine	***1***	***1.1***	***73.9***
	IROX	***1***	***1.1***	***75.0***
	Paclitaxel	***1***	***1.1***	***76.1***
	Paclitaxel protein-bound/epirubicin/carboplatin/cyclophosphamide	***1***	***1.1***	***77.3***
	Paclitaxel/trastuzumab/carboplatin/pertuzumab	***1***	***1.1***	***78.4***
	Pemetrexed	***1***	***1.1***	***79.5***
	R-BAC	***1***	***1.1***	***80.7***
	R-bendamustine	***4***	***4.5***	***85.2***
	R-BM	***1***	***1.1***	***86.4***
	R-CEOP	***1***	***1.1***	***87.5***
	R-chlorambucil	***1***	***1.1***	***88.6***
	R-COMP	***4***	***4.5***	***93.2***
	R-CVP	***1***	***1.1***	***94.3***
	R-IEV	***1***	***1.1***	***95.5***
	RCD	***1***	***1.1***	***96.6***
	Trabectedin	***1***	***1.1***	***97.7***
	Vinflunine	***1***	***1.1***	***98.9***
	XELOX	***1***	***1.1***	***100.0***
	Total	***88***	***100.0***	

The CT schedule delivered till start of secondary prophylaxis can be characterized as follows:

- The planned duration of CT cycles was 3 weeks in 136 (61.5%) out of the 221 patients for whom the question has been answered. It was 2 weeks in 32 (14.5%) patients and 4 weeks in 26 (11.8%) patients.
- The mean planned CT cycles duration was 3.76 ± 3.23 weeks (Table 10).
- The delivered number CT cycles was 1 in 99 (44.8%) out of the 221 patients for whom the question has been answered. It was 2 for 42 (19.0%) patients and 3 for 22 (10.0%) patients.
- The mean number CT cycles delivered was 2.74 ± 2.77 (Table 10).

In case of secondary prophylaxis 57 (4.3%) patients had received a previous BT in an adjuvant setting (40 patients; 3.0%), in neo-adjuvant setting (6 patients; 0.5%), in a metastatic setting (6 patients; 0.5%) or in another setting (5 patients; 0.4%; 2 relapse, 2 curative and 1 palliative settings). The list of previous BT can be found in Table 18.

Table 18 Previous biological treatments (Safety population)

		Frequency	Percent	Cumulative Percent
Valid	Trastuzumab	*10*	*17.5*	*17.5*
	Bevacizumab	*3*	*5.3*	*22.8*
	Panitumumab	*1*	*1.8*	*24.6*
	Other	*2*	*3.5*	*28.1*
	Rituximab	*41*	*71.9*	*100.0*
	Total	*57*	*100.0*	

The cross-tabulation of FN risk level as a function of the type of prophylaxis use of Lonquex can be found in Table 19.

Table 19 FN risk level as a function of the type of prophylaxis use of Lonquex (Safety population)

			Prophylactic use of Lonquex		Total
			Primary prophylaxis	Secondary prophylaxis	
FN risk	Low (<10%)	Count	*101*	*26*	*127*
		% of Total	*7.8%*	*2.0%*	*9.8%*
	Intermediate (10-20%)	Count	*364*	*118*	*482*
		% of Total	*28.1%*	*9.1%*	*37.2%*
	High (>20%)	Count	*608*	*79*	*687*
		% of Total	*46.9%*	*6.1%*	*53.0%*
Total		Count	*1073*	*223*	*1296*
		% of Total	*82.8%*	*17.2%*	*100.0%*

Timing of Lonquex administration

Overall, 897 patients started with Lonquex in primary prophylaxis at cycle 1, 110 at cycle 2, 36 at cycle 3, 20 at cycle 4, 13 at cycle 5, 9 at cycle 6, 1 at cycle 8, 1 at cycle 9 and 1 at cycle 13. A total of 19 patients started with Lonquex in secondary prophylaxis at cycle 1, 107 at cycle 2, 48 at cycle 3, 17 at cycle 4, 15 at cycle 5, 9 at cycle 6, 3 at cycle 7, 3 at cycle 8, 1 at cycle 9, 1 at cycle 10, 1 at cycle 13 and 1 at cycle 18 (Table 20).

Table 20 Number of patients starting the Lonquex treatment by cycle (Safety population)

	Number of patients starting Lonquex treatment	
	Primary prophylaxis (N=1,088)	Secondary prophylaxis (N=225)
Cycle 1	897	19
Cycle 2	110	107
Cycle 3	36	48
Cycle 4	20	17
Cycle 5	13	15
Cycle 6	9	9
Cycle 7	0	3
Cycle 8	1	3
Cycle 9	1	1
Cycle 10	0	1
Cycle 13	1	1
Cycle 18	0	1

In CT cycle 1, Lonquex was administered on time after the CT cycle (no delay; i.e. Lonquex was administered one day after the last administration of chemotherapeutic agent in the respective cycle) in 898 cycles (98.0%). The time delay went from 2 to 30 days in the 12 cycles (1.3%) where Lonquex was not administered on time after the CT cycle. The information was missing for 5 cycles (0.5%)

A total of 354 patients (27.0%) and 324 patients (24.7%) received Lonquex more than 1 day and more than 3 days after the end of the CT cycle in at least one cycle, respectively.

The number of cycles in which Lonquex was administered with a certain number of days of delay after CT end date can be found in Table 21.

Table 21 Number of days of delay of Lonquex administration after the end of CT cycles (Safety population)

		Frequency	Percentage
Valid	**1 (i.e. administration 2 days after CT end)**	***69***	***1.2***
	2	***35***	***.6***
	3	***29***	***.5***
	4	***40***	***.7***
	5	***30***	***.5***
	6	***41***	***.7***
	7	***169***	***3.0***
	8	***21***	***.4***
	9	***12***	***.2***
	10	***10***	***.2***
	11	***6***	***.1***
	12	***12***	***.2***
	13	***3***	***.1***
	14	***35***	***.6***
	15	***14***	***.2***
	16	***7***	***.1***
	17	***5***	***.1***
	18	***4***	***.1***
	20	***6***	***.1***
	21	***8***	***.1***
	22	***2***	***.0***
	23	***5***	***.1***
	24	***2***	***.0***
	25	***1***	***.0***
	28	***4***	***.1***
	29	***2***	***.0***
	30	***2***	***.0***
	33	***1***	***.0***
	35	***2***	***.0***
	36	***1***	***.0***
	40	***1***	***.0***
	42	***1***	***.0***
	49	***1***	***.0***
	70	***1***	***.0***
	77	***1***	***.0***
	Total	***583***	***10.4***

	Frequency	Percentage
No delay at all (i.e. administration one day after CT end)	***4957***	***88.4***
Missing	***67***	***1.2***
Total	***5607***	***100.0***

Additional information illustrating several parameters as a function of the primary tumour type can be found in Table 22 to Table 25.

Table 22 Age of the patient by primary tumor type (Safety population)

Primary tumor	N	Mean	Median	SD	Min	Max
Bladder	8	70.88	72.50	5.384	63	79
Blood	27	65.22	66.00	11.917	35	90
Bone	1	51.00	51.00	.	51	51
Breast	613	54.62	54.00	11.293	25	81
Brain	1	66.00	66.00	.	66	66
Cervix	3	53.33	53.00	5.508	48	59
Colon	25	62.48	62.00	8.699	48	81
Duodenum	1	61.00	61.00	.	61	61
Endometrium	15	63.00	63.00	10.603	45	80
Gallbladder	3	63.33	60.00	13.317	52	78
Germ cells	3	37.67	38.00	11.504	26	49
Head	8	57.75	60.50	6.964	44	64
Larynx	3	57.33	54.00	6.658	53	65
Lung	54	64.13	66.00	8.770	36	79
Lymphoma	347	61.50	65.00	15.841	19	95
Neck	3	51.00	57.00	11.269	38	58
Ovary	44	59.25	59.50	11.094	30	81
Pancreas	19	62.37	62.00	8.221	48	80
Prostate	40	69.38	69.50	6.979	48	82
Rectum	4	61.75	63.00	11.927	46	75
Salivary glands	3	63.00	74.00	25.357	34	81
Skin	1	64.00	64.00	.	64	64
Stomach	16	65.13	69.00	15.840	32	86
Testicle	17	40.47	40.00	11.700	21	61
Neuroendocrine	3	68.67	70.00	4.163	64	72
Vulva	1	69.00	69.00	.	69	69
Soft tissue sarcoma	2	40.00	40.00	21.213	25	55
Squamous cell cancer of the extremity	1	71.00	71.00	.	71	71
Multiple myeloma	15	68.40	68.00	7.944	53	79
Melanoma	1	66.00	66.00	.	66	66
Uterus	4	56.75	55.50	13.200	42	74
Ileum	2	61.50	61.50	10.607	54	69
Thymus	2	47.50	47.50	10.607	40	55
Oral cavity	4	51.25	51.00	10.243	39	64
Ewing sarcoma	1	38.00	38.00	.	38	38
Ethmoid sarcoma	1	71.00	71.00	.	71	71
Sclerosing epithelioid fibrosarcoma	1	54.00	54.00	.	54	54

Primary tumor	N	Mean	Median	SD	Min	Max
Uterus. peritoneum. ear	1	71.00	71.00	.	71	71
Oropharynx	1	53.00	53.00	.	53	53
Esophagogastric junction	1	64.00	64.00	.	64	64
Leiomyosarcoma	1	56.00	56.00	.	56	56
Neuroendocrine lung	1	61.00	61.00	.	61	61
Soft tissue sarcoma extremity	3	58.33	57.00	9.074	50	68
Myoepithelial	1	49.00	49.00	.	49	49
Hairy cell leukemia	2	66.50	66.50	7.778	61	72
Chronic lymphocytic leukemia	3	58.00	59.00	5.568	52	63
Trachea	1	65.00	65.00	.	65	65
Unknown	1	75.00	75.00	.	75	75
Total	1313	58.38	59.00	13.280	19	95

Table 23 Number of risks per primary tumor type (Safety population)

Primary tumor	N	Mean	Median	SD	Min	Max
Bladder	8	2.6250	2.5000	1.76777	1.00	6.00
Blood	27	2.6296	3.0000	1.71303	.00	6.00
Bone	1	.0000	.0000	.	.00	.00
Breast	613	1.6786	1.0000	.90901	.00	7.00
Brain	1	4.0000	4.0000	.	4.00	4.00
Cervix	3	2.3333	2.0000	1.52753	1.00	4.00
Colon	25	2.0000	2.0000	1.22474	.00	5.00
Duodenum	1	2.0000	2.0000	.	2.00	2.00
Endometrium	15	2.6667	2.0000	1.34519	1.00	6.00
Gallbladder	3	2.0000	2.0000	.00000	2.00	2.00
Germ cells	3	1.6667	2.0000	.57735	1.00	2.00
Head	8	1.6250	1.5000	1.40789	.00	4.00
Larynx	3	.6667	1.0000	.57735	.00	1.00
Lung	54	2.3333	2.0000	1.27383	.00	5.00
Lymphoma	347	2.3602	2.0000	1.34934	.00	6.00
Neck	3	.6667	1.0000	.57735	.00	1.00
Ovary	44	2.2955	2.0000	.95429	1.00	4.00
Pancreas	19	2.3684	2.0000	1.60591	.00	6.00
Prostate	40	2.8000	3.0000	1.39963	1.00	8.00
Rectum	4	2.7500	2.5000	.95743	2.00	4.00
Salivary glands	3	1.3333	1.0000	1.52753	.00	3.00
Skin	1	2.0000	2.0000	.	2.00	2.00
Stomach	16	3.0625	3.0000	2.20511	.00	8.00
Testicle	17	.8235	1.0000	1.01460	.00	4.00
Neuroendocrine	3	2.3333	2.0000	1.52753	1.00	4.00
Vulva	1	2.0000	2.0000	.	2.00	2.00
Soft tissue sarcoma	2	1.0000	1.0000	1.41421	.00	2.00
Squamous cell cancer of the extremity	1	2.0000	2.0000	.	2.00	2.00
Multiple myeloma	15	2.4000	2.0000	1.63881	.00	7.00
Melanoma	1	2.0000	2.0000	.	2.00	2.00
Uterus	4	2.0000	2.5000	1.41421	.00	3.00
Ileum	2	3.0000	3.0000	1.41421	2.00	4.00
Thymus	2	1.5000	1.5000	.70711	1.00	2.00
Oral cavity	4	1.5000	1.5000	1.29099	.00	3.00
Ewing sarcoma	1	4.0000	4.0000	.	4.00	4.00
Ethmoid sarcoma	1	3.0000	3.0000	.	3.00	3.00
Sclerosing epithelioid fibrosarcoma	1	2.0000	2.0000	.	2.00	2.00

Primary tumor	N	Mean	Median	SD	Min	Max
Uterus. peritoneum. ear	1	3.0000	3.0000	.	3.00	3.00
Oropharynx	1	.0000	.0000	.	.00	.00
Esophagogastric junction	1	4.0000	4.0000	.	4.00	4.00
Leiomyosarcoma	1	4.0000	4.0000	.	4.00	4.00
Neuroendocrine lung	1	.0000	.0000	.	.00	.00
Soft tissue sarcoma extremity	3	2.3333	2.0000	1.52753	1.00	4.00
Myoepithelial	1	1.0000	1.0000	.	1.00	1.00
Hairy cell leukemia	2	1.5000	1.5000	.70711	1.00	2.00
Chronic lymphocytic leukemia	3	1.0000	1.0000	.00000	1.00	1.00
Trachea	1	2.0000	2.0000	.	2.00	2.00
Unknown	1	2.0000	2.0000	.	2.00	2.00
Total	1313	2.0160	2.0000	1.23178	.00	8.00

Table 24 Setting of CT use as a function of primary tumor type (Safety population)

	Adjuvant or metastatic use of CT									
	Adjuvant setting/Induction		Neo-adjuvant setting/Consolidation		Metastatic setting		Maintenance		Other setting	
	Count	%	Count	%	Count	%	Count	%	Count	%
Bladder	*1*	*12.5%*	*2*	*25.0%*	*4*	*50.0%*	*1*	*12.5%*	*0*	*0.0%*
Blood	*18*	*81.8%*	*0*	*0.0%*	*0*	*0.0%*	*4*	*18.2%*	*0*	*0.0%*
Bone	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Breast	*323*	*53.5%*	*223*	*36.9%*	*54*	*8.9%*	*0*	*0.0%*	*4*	*0.7%*
Brain	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Cervix	*0*	*0.0%*	*0*	*0.0%*	*2*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Colon	*10*	*40.0%*	*0*	*0.0%*	*15*	*60.0%*	*0*	*0.0%*	*0*	*0.0%*
Duodenum	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Endometrium	*8*	*57.1%*	*0*	*0.0%*	*6*	*42.9%*	*0*	*0.0%*	*0*	*0.0%*
Gallbladder	*2*	*66.7%*	*0*	*0.0%*	*0*	*0.0%*	*1*	*33.3%*	*0*	*0.0%*
Germ cells	*0*	*0.0%*	*0*	*0.0%*	*3*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Head	*1*	*12.5%*	*2*	*25.0%*	*5*	*62.5%*	*0*	*0.0%*	*0*	*0.0%*
Larynx	*0*	*0.0%*	*1*	*50.0%*	*0*	*0.0%*	*0*	*0.0%*	*1*	*50.0%*
Lung	*3*	*5.6%*	*2*	*3.7%*	*47*	*87.0%*	*2*	*3.7%*	*0*	*0.0%*
Lymphoma	*304*	*87.6%*	*11*	*3.2%*	*5*	*1.4%*	*7*	*2.0%*	*20*	*5.8%*
Neck	*0*	*0.0%*	*1*	*33.3%*	*1*	*33.3%*	*1*	*33.3%*	*0*	*0.0%*
Ovary	*18*	*43.9%*	*3*	*7.3%*	*18*	*43.9%*	*1*	*2.4%*	*1*	*2.4%*
Pancreas	*0*	*0.0%*	*0*	*0.0%*	*17*	*89.5%*	*1*	*5.3%*	*1*	*5.3%*
Prostate	*1*	*2.6%*	*0*	*0.0%*	*38*	*97.4%*	*0*	*0.0%*	*0*	*0.0%*
Rectum	*1*	*25.0%*	*0*	*0.0%*	*3*	*75.0%*	*0*	*0.0%*	*0*	*0.0%*
Salivary glands	*1*	*33.3%*	*0*	*0.0%*	*1*	*33.3%*	*1*	*33.3%*	*0*	*0.0%*
Skin	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Stomach	*3*	*20.0%*	*4*	*26.7%*	*7*	*46.7%*	*1*	*6.7%*	*0*	*0.0%*
Testicle	*12*	*70.6%*	*0*	*0.0%*	*1*	*5.9%*	*0*	*0.0%*	*4*	*23.5%*
Neuroendocrine	*0*	*0.0%*	*0*	*0.0%*	*2*	*66.7%*	*1*	*33.3%*	*0*	*0.0%*
Vulva	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Soft tissue sarcoma	*1*	*50.0%*	*0*	*0.0%*	*1*	*50.0%*	*0*	*0.0%*	*0*	*0.0%*
Squamous cell cancer of the extremity	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Multiple myeloma	*11*	*73.3%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*4*	*26.7%*

	Adjuvant or metastatic use of CT									
	Adjuvant setting/Induction		Neo-adjuvant setting/Consolidation		Metastatic setting		Maintenance		Other setting	
	Count	%	Count	%	Count	%	Count	%	Count	%
Melanoma	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Uterus	*0*	*0.0%*	*0*	*0.0%*	*4*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Ileum	*1*	*50.0%*	*0*	*0.0%*	*1*	*50.0%*	*0*	*0.0%*	*0*	*0.0%*
Thymus	*1*	*50.0%*	*0*	*0.0%*	*1*	*50.0%*	*0*	*0.0%*	*0*	*0.0%*
Oral cavity	*1*	*25.0%*	*0*	*0.0%*	*2*	*50.0%*	*0*	*0.0%*	*1*	*25.0%*
Ewing sarcoma	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Ethmoid sarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Sclerosing epithelioid fibrosarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Uterus. peritoneum. ear	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Oropharynx	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Esophagogastric junction	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Leiomyosarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Neuroendocrine lung	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Soft tissue sarcoma extremity	*1*	*33.3%*	*1*	*33.3%*	*1*	*33.3%*	*0*	*0.0%*	*0*	*0.0%*
Myoepithelial	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Hairy cell leukemia	*2*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Chronic lymphocytic leukemia	*3*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Trachea	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*	*0*	*0.0%*
Total	*731*	*56.7%*	*253*	*19.6%*	*247*	*19.1%*	*22*	*1.7%*	*37*	*2.9%*

Table 25 FN risk as a function of the primary tumor type (Safety population)

	FN risk					
	Low (<10%)		Intermediate (10-20%)		High (>20%)	
	Count	%	Count	%	Count	%
Bladder	*1*	*12.5%*	*4*	*50.0%*	*3*	*37.5%*
Blood	*2*	*9.1%*	*7*	*31.8%*	*13*	*59.1%*
Bone	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Breast	*79*	*13.0%*	*185*	*30.4%*	*344*	*56.6%*
Brain	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Cervix	*0*	*0.0%*	*1*	*50.0%*	*1*	*50.0%*
Colon	*1*	*4.0%*	*19*	*76.0%*	*5*	*20.0%*
Duodenum	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Endometrium	*1*	*6.7%*	*7*	*46.7%*	*7*	*46.7%*
Gallbladder	*0*	*0.0%*	*3*	*100.0%*	*0*	*0.0%*
Germ cells	*0*	*0.0%*	*1*	*33.3%*	*2*	*66.7%*
Head	*0*	*0.0%*	*0*	*0.0%*	*8*	*100.0%*
Larynx	*0*	*0.0%*	*1*	*50.0%*	*1*	*50.0%*
Lung	*1*	*1.9%*	*27*	*50.0%*	*26*	*48.1%*
Lymphoma	*31*	*8.9%*	*134*	*38.6%*	*182*	*52.4%*
Neck	*0*	*0.0%*	*1*	*33.3%*	*2*	*66.7%*
Ovary	*0*	*0.0%*	*25*	*61.0%*	*16*	*39.0%*
Pancreas	*2*	*10.5%*	*10*	*52.6%*	*7*	*36.8%*
Prostate	*1*	*2.6%*	*21*	*53.8%*	*17*	*43.6%*
Rectum	*0*	*0.0%*	*2*	*50.0%*	*2*	*50.0%*
Salivary glands	*1*	*33.3%*	*1*	*33.3%*	*1*	*33.3%*
Skin	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Stomach	*0*	*0.0%*	*9*	*60.0%*	*6*	*40.0%*
Testicle	*2*	*11.8%*	*3*	*17.6%*	*12*	*70.6%*
Neuroendocrine	*0*	*0.0%*	*1*	*33.3%*	*2*	*66.7%*
Vulva	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Soft tissue sarcoma	*0*	*0.0%*	*0*	*0.0%*	*2*	*100.0%*
Squamous cell cancer of the extremity	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Multiple myeloma	*1*	*6.7%*	*7*	*46.7%*	*7*	*46.7%*
Melanoma	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Uterus	*0*	*0.0%*	*2*	*50.0%*	*2*	*50.0%*
Ileum	*0*	*0.0%*	*1*	*50.0%*	*1*	*50.0%*
Thymus	*0*	*0.0%*	*0*	*0.0%*	*2*	*100.0%*
Oral cavity	*0*	*0.0%*	*1*	*25.0%*	*3*	*75.0%*
Ewing sarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*

	FN risk					
	Low (<10%)		Intermediate (10-20%)		High (>20%)	
	Count	%	Count	%	Count	%
Ethmoid sarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Sclerosing epithelioid fibrosarcoma	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Uterus. peritoneum. ear	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Oropharynx	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Esophagogastric junction	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Leiomyosarcoma	*0*	*0.0%*	*0*	*0.0%*	*1*	*100.0%*
Neuroendocrine lung	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Soft tissue sarcoma extremity	*1*	*33.3%*	*0*	*0.0%*	*2*	*66.7%*
Myoepithelial	*1*	*100.0%*	*0*	*0.0%*	*0*	*0.0%*
Hairy cell leukemia	*0*	*0.0%*	*1*	*50.0%*	*1*	*50.0%*
Chronic lymphocytic leukemia	*0*	*0.0%*	*1*	*33.3%*	*2*	*66.7%*
Trachea	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Unknown	*0*	*0.0%*	*1*	*100.0%*	*0*	*0.0%*
Total	*127*	*9.8%*	*482*	*37.2%*	*687*	*53.0%*

6.3. Comorbidities

Overall, in the safety population and in patients in whom the comorbidities had been evaluated (N=1296), 733 patients (56.6%) had at least one System Organ Class (SOC) affected.

The mean number of SOCs affected per patient was 1.10 ± 1.29 with a minimum of 0 and a maximum of 7.

A total of 353 (27.3%) patients had 1 SOC affected, 188 (14.5%) patients had 2 SOCs affected, 112 (8.7%) had 3 SOCs affected, 54 (4.2%) had 4 SOCs affected and 19 (1.5%) patient had 5 SOCs affected.

A cardiovascular comorbidity was found in 396 (30.6%) patients. The information is missing for 6 patients (0.5%).

A CNS comorbidity was found in 46 (3.5%) patients. The information was missing for 7 patients (0.5%).

A digestive comorbidity was found in 117 (9.0%) patients. The information was missing for 7 patients (0.5%).

An endocrine comorbidity was found in 218 (16.8%) patients. The information was missing for 5 patients (0.4%).

A genitourinary comorbidity was found in 111 (8.6%) patients. The information was missing for 6 patients (0.5%).

A musculoskeletal comorbidity was found in 104 (8.0%) patients. The information was missing for 6 patients (0.5%).

A peripheral nervous system comorbidity was found in 36 (2.8%) patients. The information was missing for 7 patients (0.5%).

A respiratory comorbidity was found in 103 (7.9%) patients. The information was missing for 7 patients (0.5%).

Other types of comorbidities were found in 288 (22.2%) patients. The information was missing for 7 patients (0.5%).

The distribution of the number of SOCs as a function of the primary tumour can be found in Table 26.

Table 26 Number of SOCs affected as a function of the primary tumor (Safety population)

			Number of SOCs affected							
			0	1	2	3	4	5	6	7
Primary tumor	Bladder	Count	5	0	2	1	0	0	0	0
		%	0.9%	0.0%	1.1%	0.9%	0.0%	0.0%	0.0%	0.0%
	Blood	Count	6	6	3	5	2	0	0	0
		%	1.1%	1.7%	1.6%	4.5%	3.7%	0.0%	0.0%	0.0%
	Bone	Count	0	1	0	0	0	0	0	0
		%	0.0%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Breast	Count	302	153	73	43	22	11	2	1
		%	53.8%	43.3%	38.8%	38.4%	40.7%	57.9%	33.3%	100.0%
	Brain	Count	0	0	0	1	0	0	0	0
		%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%	0.0%	0.0%
	Cervix	Count	0	1	0	1	0	0	0	0
		%	0.0%	0.3%	0.0%	0.9%	0.0%	0.0%	0.0%	0.0%
	Colon	Count	10	10	4	1	0	0	0	0
		%	1.8%	2.8%	2.1%	0.9%	0.0%	0.0%	0.0%	0.0%
	Duodenum	Count	1	0	0	0	0	0	0	0
		%	0.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Endometrium	Count	4	4	3	1	1	0	2	0
		%	0.7%	1.1%	1.6%	0.9%	1.9%	0.0%	33.3%	0.0%
	Gallbladder	Count	2	0	1	0	0	0	0	0
		%	0.4%	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%
	Germ cells	Count	3	0	0	0	0	0	0	0
		%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Head	Count	3	3	1	1	0	0	0	0
		%	0.5%	0.8%	0.5%	0.9%	0.0%	0.0%	0.0%	0.0%
	Larynx	Count	1	0	0	1	0	0	0	0
		%	0.2%	0.0%	0.0%	0.9%	0.0%	0.0%	0.0%	0.0%
	Lung	Count	17	15	8	8	4	0	1	0
		%	3.0%	4.2%	4.3%	7.1%	7.4%	0.0%	16.7%	0.0%
	Lymphoma	Count	121	103	59	36	21	6	1	0
		%	21.6%	29.2%	31.4%	32.1%	38.9%	31.6%	16.7%	0.0%
	Neck	Count	3	0	0	0	0	0	0	0
		%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
	Ovary	Count	21	10	10	0	0	0	0	0
		%	3.7%	2.8%	5.3%	0.0%	0.0%	0.0%	0.0%	0.0%
	Pancreas	Count	8	5	4	2	0	0	0	0

			Number of SOCs affected							
			0	1	2	3	4	5	6	7
		%	*1.4%*	*1.4%*	*2.1%*	*1.8%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Prostate	**Count**	*15*	*14*	*7*	*3*	*0*	*0*	*0*	*0*
		%	*2.7%*	*4.0%*	*3.7%*	*2.7%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Rectum	**Count**	*3*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.5%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Salivary glands	**Count**	*1*	*2*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.6%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Skin	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Stomach	**Count**	*5*	*1*	*3*	*4*	*1*	*1*	*0*	*0*
		%	*0.9%*	*0.3%*	*1.6%*	*3.6%*	*1.9%*	*5.3%*	*0.0%*	*0.0%*
	Testicle	**Count**	*8*	*6*	*3*	*0*	*0*	*0*	*0*	*0*
		%	*1.4%*	*1.7%*	*1.6%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Neuroendocrine	**Count**	*0*	*1*	*1*	*1*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.5%*	*0.9%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Vulva	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Soft tissue sarcoma	**Count**	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.4%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Squamous cell cancer of the extremity	**Count**	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*
		%	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*1.9%*	*0.0%*	*0.0%*	*0.0%*
	Multiple myeloma	**Count**	*6*	*4*	*1*	*3*	*1*	*0*	*0*	*0*
		%	*1.1%*	*1.1%*	*0.5%*	*2.7%*	*1.9%*	*0.0%*	*0.0%*	*0.0%*
	Melanoma	**Count**	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Uterus	**Count**	*2*	*0*	*2*	*0*	*0*	*0*	*0*	*0*
		%	*0.4%*	*0.0%*	*1.1%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Ileum	**Count**	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Thymus	**Count**	*0*	*1*	*0*	*0*	*0*	*1*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*5.3%*	*0.0%*	*0.0%*
	Oral cavity	**Count**	*4*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.7%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Ewing sarcoma	**Count**	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Ethmoid sarcoma	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*

			Number of SOCs affected							
			0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Sclerosing epithelioid fibrosarcoma	**Count**	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Uterus. peritoneum. ear	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Oropharynx	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Esophagogastric junction	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Leiomyosarcoma	**Count**	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Neuroendocrine lung	**Count**	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Soft tissue sarcoma extremity	**Count**	*1*	*2*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.6%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Myoepithelial	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Hairy cell leukemia	**Count**	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*
		%	*0.2%*	*0.0%*	*0.5%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Chronic lymphocytic leukemia	**Count**	*0*	*1*	*1*	*0*	*1*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.5%*	*0.0%*	*1.9%*	*0.0%*	*0.0%*	*0.0%*
	Trachea	**Count**	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
	Unknown	**Count**	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*
		%	*0.0%*	*0.0%*	*0.5%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Total		**Count**	*561*	*353*	*188*	*112*	*54*	*19*	*6*	*1*
		%	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*	*100.0%*

7. EFFICACY RESULTS

7.1. Quality of Life: QLQ-C30

The evolution of the quality of life measured with the QLQ-C30 scale between baseline, cycles and study conclusion can be found in Table 27.

Table 27 Evolution of the quality of life from baseline to study conclusion: QLQ-C30 scores (Efficacy population)

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
Global health status QoL score at baseline	*1182*	*81*	*60.7375*	*66.6667*	*22.53543*	*.00*	*100.00*
Global health status QoL score during cycles	*736*	*527*	*59.8053*	*66.6667*	*20.60828*	*.00*	*100.00*
Global health status QoL score at conclusion	*790*	*473*	*61.6667*	*66.6667*	*21.76386*	*.00*	*100.00*
Physical functioning score at baseline	*1196*	*67*	*78.4281*	*86.6667*	*22.02362*	*.00*	*100.00*
Physical functioning score during cycles	*744*	*519*	*74.3728*	*80.0000*	*20.74728*	*.00*	*100.00*
Physical functioning score at study conclusion	*795*	*468*	*74.6611*	*80.0000*	*21.44697*	*.00*	*100.00*
Role functioning score at baseline	*1186*	*77*	*71.3322*	*83.3333*	*29.99868*	*.00*	*100.00*
Role functioning score during cycles	*741*	*522*	*65.6995*	*66.6667*	*28.54390*	*.00*	*100.00*
Role functioning score at study conclusion	*794*	*469*	*67.4433*	*66.6667*	*29.09881*	*.00*	*100.00*
Emotional functioning score at baseline	*1190*	*73*	*72.1078*	*75.0000*	*23.00071*	*.00*	*100.00*
Emotional functioning score during cycles	*744*	*519*	*76.1051*	*83.3333*	*21.66717*	*.00*	*100.00*
Emotional functioning score at study conclusion	*796*	*467*	*75.6107*	*83.3333*	*21.74597*	*.00*	*100.00*
Cognitive functioning score at baseline	*1192*	*71*	*84.9553*	*100.0000*	*20.00974*	*.00*	*100.00*
Cognitive functioning score during cycles	*743*	*520*	*82.5707*	*83.3333*	*22.23345*	*.00*	*100.00*
Cognitive functioning score at study conclusion	*798*	*465*	*83.1871*	*83.3333*	*20.74638*	*.00*	*100.00*
Social functioning score at baseline	*1186*	*77*	*76.9533*	*83.3333*	*26.68692*	*.00*	*100.00*
Social functioning score during cycles	*739*	*524*	*73.3875*	*66.6667*	*25.88273*	*.00*	*100.00*
Social functioning score at study conclusion	*795*	*468*	*74.2138*	*83.3333*	*26.81282*	*.00*	*100.00*
Fatigue score at baseline	*1195*	*68*	*34.6258*	*33.3333*	*25.84737*	*.00*	*100.00*
Fatigue score during cycles	*742*	*521*	*41.3896*	*33.3333*	*25.81187*	*.00*	*100.00*
Fatigue score at study conclusion	*796*	*467*	*38.3166*	*33.3333*	*24.55090*	*.00*	*100.00*
Nausea and vomiting score at baseline	*1195*	*68*	*8.3821*	*.0000*	*16.58789*	*.00*	*100.00*

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
Nausea and vomiting score during cycles	*743*	*520*	*11.8439*	*.0000*	*18.24086*	*.00*	*100.00*
Nausea and vomiting score at study conclusion	*797*	*466*	*8.4693*	*.0000*	*16.74184*	*.00*	*100.00*
Pain score at baseline	*1196*	*67*	*23.2023*	*16.6667*	*27.42254*	*.00*	*100.00*
Pain score during cycles	*744*	*519*	*22.5134*	*16.6667*	*26.52158*	*.00*	*100.00*
Pain score at study conclusion	*798*	*465*	*25.4386*	*16.6667*	*28.75833*	*.00*	*100.00*
Dyspnoea score at baseline	*1191*	*72*	*17.1285*	*.0000*	*25.04005*	*.00*	*100.00*
Dyspnoea score during cycles	*737*	*526*	*21.8905*	*.0000*	*26.18419*	*.00*	*100.00*
Dyspnoea score at study conclusion	*790*	*473*	*20.4641*	*.0000*	*26.56844*	*.00*	*100.00*
Insomnia score at baseline	*1184*	*79*	*29.2793*	*33.3333*	*30.09778*	*.00*	*100.00*
Insomnia score during cycles	*740*	*523*	*27.5676*	*33.3333*	*29.21978*	*.00*	*100.00*
Insomnia score at study conclusion	*792*	*471*	*24.7475*	*33.3333*	*28.33227*	*.00*	*100.00*
Loss of appetite score at baseline	*1188*	*75*	*18.3221*	*.0000*	*27.40056*	*.00*	*100.00*
Loss of appetite score during cycles	*739*	*524*	*20.8841*	*.0000*	*27.62615*	*.00*	*100.00*
Loss of appetite score at study conclusion	*795*	*468*	*16.1006*	*.0000*	*25.10880*	*.00*	*100.00*
Constipation score at baseline	*1169*	*94*	*15.3693*	*.0000*	*26.14354*	*.00*	*100.00*
Constipation score during cycles	*735*	*528*	*15.4195*	*.0000*	*25.05583*	*.00*	*100.00*
Constipation score at study conclusion	*783*	*480*	*12.4308*	*.0000*	*22.20785*	*.00*	*100.00*
Diarrhoea score at baseline	*1188*	*75*	*8.0808*	*.0000*	*19.78500*	*.00*	*100.00*
Diarrhoea score during cycles	*743*	*520*	*10.9017*	*.0000*	*21.03656*	*.00*	*100.00*
Diarrhoea score at study conclusion	*797*	*466*	*8.1138*	*.0000*	*18.48453*	*.00*	*100.00*
Financial difficulties score at baseline	*1173*	*90*	*16.2546*	*.0000*	*26.39852*	*.00*	*100.00*
Financial difficulties score during cycles	*731*	*532*	*16.3703*	*.0000*	*26.48029*	*.00*	*100.00*
Financial difficulties score at study conclusion	*788*	*475*	*17.9357*	*.0000*	*26.67137*	*.00*	*100.00*

7.2. Quality of Life: Brief Pain Inventory (BPI)

The evolution of the quality of life measured with the BPI scale, between baseline, cycles and study conclusion can be found in Table 28.

Table 28 Evolution of the quality of life from baseline to study conclusion: BPI scores (Efficacy population)

	N		Mean	Median	SD	Min	Max
	Valid	Missing					
Pain score at baseline	*1073*	*186*	*1.7833*	*.6667*	*2.21582*	*.00*	*10.00*
Pain score during cycles	*678*	*581*	*1.6008*	*.6667*	*2.03643*	*.00*	*9.00*
Pain score at study conclusion	*718*	*541*	*1.9097*	*1.0000*	*2.31137*	*.00*	*10.00*
Pain relief score at baseline	*594*	*665*	*41.3805*	*40.0000*	*37.58000*	*.00*	*100.00*
Pain relief score during cycles	*364*	*895*	*39.9148*	*40.0000*	*37.37600*	*.00*	*100.00*
Pain relief score at study conclusion	*414*	*845*	*40.6039*	*40.0000*	*35.25586*	*.00*	*100.00*
Activity score at baseline	*988*	*271*	*1.8961*	*.5000*	*2.48758*	*.00*	*10.00*
Activity score during cycles	*633*	*626*	*2.0517*	*.7500*	*5.54377*	*.00*	*100.00*
Activity score at study conclusion	*669*	*590*	*2.0159*	*1.0000*	*2.47052*	*.00*	*10.00*
Mood and relation score at baseline	*986*	*273*	*1.7720*	*.6667*	*2.45746*	*.00*	*10.00*
Mood and relation score during cycles	*633*	*626*	*1.6940*	*.3333*	*2.77394*	*.00*	*30.00*
Mood and relation score at study conclusion	*669*	*590*	*1.9083*	*.6667*	*2.43148*	*.00*	*10.00*
Pain interference score at baseline	*988*	*271*	*1.8373*	*.6667*	*2.40482*	*.00*	*10.00*
Pain interference score during cycles	*635*	*624*	*1.8709*	*.7917*	*3.48144*	*.00*	*50.00*
Pain interference score at study conclusion	*669*	*590*	*1.9621*	*.9167*	*2.37548*	*.00*	*9.75*

7.3. Chemotherapy dose modifications (all cycles)

This analysis included data recorded in eCRFs in all cycles following the cycles in which Lonquex had been administered, exploring the impact of Lonquex administration on the dose delivery in the following cycle.

This cohort was constituted of 4,292 cycles in 1,160 patients (a mean of 3.70 cycles/patient).

Lonquex was used as:

- PP in 3,748 cycles (87.3%) in 972 patients (83.8%) or
- SP in 544 cycles (12.7%) in 188 patients (16.2%).
- No information was missing.

Chemotherapy modifications

Number of patients and cycles in which chemotherapy omissions, delays and reductions were reported is shown in Table 29. The results are shown for all patients as well as for those receiving Lonquex in primary and secondary prophylaxis.

Table 29 Number of cycles and number of patients with chemotherapy omissions, delays and reductions (Efficacy population)

	Total		PP		SP	
	Cycles N=4292	Patients N=1160	Cycles N=3748	Patients N=972	Cycles N=1544	Patients N=188
CT omission						
N (%)	16 (0.4)	15 (1.3)	13 (0.3)	12 (1.2)	3 (0.6)	3 (1.6)
Missing data: n (%)	34 (0.8)	16 (1.4)	32 (0.9)	14 (1.4)	2 (0.4)	2 (1.1)
CT delay						
N (%)	512 (11.9)	350 (30.2)	428 (11.4)	292 (30.0)	84 (15.4)	58 (30.9)
Missing data: n (%)	49 (1.1)	29 (2.5)	44 (1.2)	24 (2.5)	5 (0.9)	5 (2.7)
CT reduction						
N (%)	404 (9.4)	179 (15.4)	317 (8.5)	140 (14.4)	87 (16.0)	39 (20.7)
Missing data: n (%)	46 (1.1)	20 (1.7)	42 (1.1)	17 (1.7)	4 (0.3)	3 (1.6)

In cycles where chemotherapy was delayed **the mean CT delay** was:

- All patients (n=512 delayed cycles): 7.8 ± 7.2 days
- Primary prophylaxis (n=428 delayed cycles): 7.6 ± 7.4 days
- Secondary prophylaxis (n=84 delayed cycles): 8.7 ± 6.2 days

In cycles where chemotherapy was reduced, **the mean CT dose reduction** per cycle was:

- All patients (n=404 cycles with CT reductions): -16.2 ± 16.4%
- Primary prophylaxis (n=317 cycles with CT reduction): -16.0 ± 17.2%.
- Secondary prophylaxis (n=87 cycles with CT reduction): -17.0 ± 13.0%

Biological treatment dose modifications

All (primary prophylaxis and secondary prophylaxis)

No BT was administered in 2,909 cycles (67.8%) in 839 patients (72.3%). A BT was administered in 1,383 cycles (32.2%) in 358 patients (30.9%). BT was not omitted in 1,366 (31.8%) cycles in 357 patients (30.8%). BT was omitted in 16 (0.4%) cycles in 13 patients (1.1%). One dose only was omitted in 10 cycles, two doses in 1 cycle and 6 doses in 2 cycles. No BT dose reduction was applied for 1,359 cycles (31.7%) in 357 patients (30.8%) The BT dose was reduced in 23 (0.5%) cycles in 17 patients (1.5%).

Primary prophylaxis

No BT was administered in 2,545 cycles (67.9%) in 703 patients (72.3%). A BT was administered in 1,203 cycles (32.1%) in 302 patients (31.1%). BT was not omitted in 1,189 cycles (31.7%) in 301 patients (31.0%). BT was omitted in 14 (0.4%) cycles in 11 patients (1.1%). One dose was omitted in 8 cycles, two doses in 1 cycle and 6 doses in 2 cycles. The BT dose was not reduced in 1,181 cycles (31.5%) in 301 patients (31.0%). The BT dose was reduced in 22 (0.6%) cycles in 16 patients (1.6%).

Secondary prophylaxis

No BT was administered in 364 cycles (66.9%) in 136 patients (72.3%). A BT was administered in 180 cycles (33.1%) in 56 patients (29.8%). BT was not omitted for 177 cycles (32.5%) in 56 patients (29.8%). BT was omitted in 2 cycles (0.4%) in 2 patients (1.1%). One dose only was omitted in those 2 cycles. The BT dose was not reduced in 178 cycles (32.7%) in 56 patients (29.8%). The BT dose was reduced in 1 cycle (0.2%) in 1 patient (0.5%).

Overall CT and BT dose modifications and correlation with neutropenic events

Number of CT/BT omissions, delay and reductions have been recorded, however they can be associated with a smaller number of febrile neutropenia and neutropenia (Table 30), suggesting that there might be other reasons for observed dose modifications (e.g. logistics).

Table 30 Overall CT and BT dose modifications and correlation with neutropenic events (Efficacy population)

	Total		PP		SP	
	Cycles N=4292	Patients N=1160	Cycles n=3748	Patients N=972	Cycles N=1544	Patients N=188
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CT/BT delay, reduction or omission	895 (20.9)	480 (41.4)	730 (19.5)	392 (40.3)	165 (30.3)	88 (46.8)
- **Febrile neutropenia in these* cycles**	20 (2.2)	20 (4.2)	12 (1.6)	12 (3.1)	8 (4.8)	8 (9.1)
- **Neutropenia in these* cycles**	102 (11.4)	77 (16.0)	75 (10.3)	56 (14.3)	27 (16.4)	21 (23.9)
- **Grade III neutropenia in these* cycles**	25 (2.8)	77 (16.0)	16 (2.2)	15 (3.8)	9 (5.5)	8 (9.1)
- **Grade IV neutropenia in these* cycles**	40 (4.5)	33 (6.9)	30 (4.1)	24 (6.1)	10 (37.0)	9 (10.2)
Overlap of CT/BT dose modification and FN	20 (0.4)	20 (1.7)	12 (0.3)	12 (1.2)	8 (0.5)	8 (4.3)
Overlap of CT/BT dose modification and neutropenia	102 (2.3)	77 (6.6)	75 (2.0)	56 (5.8)	27 (1.7)	21 (11.2)
Overlap of CT/BT dose modification and grade III neutropenia	25 (0.5)	77 (6.6)	16 (0.4)	15 (1.5)	9 (0.6)	8 (4.3)
Overlap of CT/BT dose modification and grade IV neutropenia	40 (0.9)	33 (2.8)	30 (0.8)	24 (2.5)	10 (0.6)	9 (4.8)

**Cycles in which CT/BT dose omission, reduction or delay were reported*

7.4. Neutropenia and related events (all cycles)

The incidence of neutropenia and related events was analysed in the cycles when Lonquex was administered.

Operationally, if neutropenia occurred in the cycle when Lonquex was administered, in eCRF it was recorded in the following cycle. E.g. if neutropenia occurred in cycle 1, it was recorded in cycle 2. However, in this report it is presented as neutropenia in cycle 1.

This cohort was constituted of 5,910 cycles in 1,305 patients (a mean of 4.53 cycles/patient).

Lonquex was used as:

- PP in 5,063 cycles (85.7%) in 1,080 patients (82.8%)
- SP in 847 cycles (14.3%) in 225 patients (17.2%)
- No information was missing.

The neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered can be found in Table 31.

Table 31 Neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered (Efficacy population)

	Total		PP		SP	
	Cycles N=5910	Patients N=1305	Cycles N=5063	Patients N=1080	Cycles N=847	Patients N=225
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Febrile neutropenia	58 (1.0)	52 (4.0)	39 (0.8)	34 (3.1)	19 (2.2)	18 (8.0)
Missing	85 (1.4)	85 (6.5)	75 (1.5)	75 (6.9)	10 (1.2)	10 (4.4)
Neutropenia	441 (7.5)	270 (20.7)	342 (6.8)	209 (19.4)	99 (11.7)	61 (27.1)
Missing	85 (1.4)	85 (6.5)	74 (1.5)	74 (6.9)	11 (1.3)	11 (4.9)
Grade III neutropenia	113 (1.9)	91 (7.0)	77 (1.5)	63 (5.8)	36 (4.3)	28 (12.4)
Grade IV neutropenia	134 (2.3)	102 (7.8)	111 (2.2)	82 (7.6)	23 (2.7)	20 (8.9)
Anti-infective	1117 (18.9)	398 (30.5)	1023 (20.2)	351 (32.5)	94 (11.1)	47 (20.9)
Missing	84 (1.4)	84 (6.4)	74 (1.5)	74 (6.9)	10 (1.2)	10 (4.4)
Anti-mycotic	349 (5.9)	131 (10.0)	306 (6.0)	113 (10.5)	43 (5.1)	18 (8.0)
Missing	84 (1.4)	84 (6.4)	74 (1.5)	74 (6.9)	10 (1.2)	10 (4.4)

	Total		PP		SP	
	Cycles N=5910	**Patients N=1305**	**Cycles N=5063**	**Patients N=1080**	**Cycles N=847**	**Patients N=225**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hospitalization	210 (3.6)	176 (13.5)	183 (3.6)	151 (14.0)	27 (3.2)	25 (11.1)
Missing	84 (1.4)	84 (6.4)	74 (1.5)	74 (6.9)	10 (1.2)	10 (4.4)
Blood transfusion	151 (2.6)	106 (8.1)	136 (2.7)	91 (8.4)	15 (1.8)	15 (6.7)
Missing	87 (1.5)	87 (6.7)	75 (1.5)	75 (6.9)	12 (1.4)	12 (5.3)
Death	18 (0.3)	18 (1.4)	17 (0.3)	17 (1.6)	1 0.1)	1 (0.4)
Missing	85 (1.4)	85 (6.5)	75 (1.5)	75 (6.9)	10 (1.2)	10 (4.4)

All cycles

The reason for using anti-infectives was FN in 29 cycles (2.9%; 27 patients [2.1%]), CIN in 29 cycles (2.6%; 21 patients [1.6%]) or another reason in 1,058 cycles (94.8%; 370 patients [28.4%]). In the majority of cycles (78.4%) this other reason was the prophylaxis of infection. The route of anti-infectives was oral in 1,029 cycles (92.2%) in 348 patients (26.7%) and IV in 87 cycles (7.8%) in 72 patients (5.5%). Anti-infectives use duration was 27.6 ± 50.4 days.

The reason for using anti-mycotics was FN in 7 cycles (2.0%; 5 patients [0.4%]), CIN in 9 cycles (2.6%; 9 patients [0.7%]) or another reason in 333 cycles (95.4%; 121 patients [9.3%]). In the majority of cycles (72.0%), prophylaxis of infection was the reason evoked for prescribing anti-mycotics. The route of anti-mycotics was oral in 331 cycles (94.8%) in 123 patients (9.4%), and IV in 18 cycles (5.2%) in 11 patients (0.8%). Anti-mycotics use duration was 24.0 ± 39.0 days.

The mean duration of hospitalization was 8.8 ± 9.2 days and the mean number of days spent in ICU was 0.51 ± 3.17 days. The reasons for hospitalisation were FN in 28 cycles (0.5%) in 27 patients (2.1%), CIN in 6 cycles (0.1%) in 6 patients (0.5%), infection in 42 cycles (0.7%) in 39 patients (3.0%), fever in 14 cycles (0.2%) in 13 patients (1.0%) and another reason in 120 cycles (2.0%) in 110 patients (8.4%).

Primary prophylaxis

The reason for using anti-infectives was FN in 22 cycles (2.2%; 20 patients [1.9%]), CIN in 24 cycles (2.3%; 16 patients [1.5%]) and another reason in 976 cycles (95.5%; 331 patients [30.6%]). In the majority of cycles (79%) this other reason was the prophylaxis of infection. The route of anti-infectives was oral in 945 cycles (92.5%) in 309 patients (28.6%), and IV in 77 cycles (7.5%) in 62 patients (5.7%). The duration of anti-infectives use was 27.8 ± 49.9 days.

The reason for using anti-mycotics was FN in 3 cycles (1.0%; 3 patients [0.3%]), CIN in 5 cycles (1.6%; 5 patients [0.5%]) or another reason in 298 cycles (97.4%; 106 patients [9.8%]). In the majority of cycles (74%), prophylaxis of infection was the reason evoked for prescribing anti-mycotics. The route of anti-mycotics was oral in 288 cycles (94.1%) in 105 patients (9.7%), or IV in 18 cycles (5.9%) in 11 patients (1.0%). The duration of anti-mycotics use was 24.4 ± 40.1 days.

The mean duration of hospitalization was 8.91 ± 9.34 days and the mean number of days spent in ICU was 0.20 ± 1.27 day. The reasons for hospitalisation were FN in 18 cycles (0.4%) in 17 patients (1.6%), CIN in 4 cycles (0.1%) in 4 patients (0.4%), infection in 39 cycles (0.8%) in 36 patients (3.3%), fever in 12 cycles (0.2%) in 11 patients (1.0%) and another reason in 110 cycles (2.2%) in 100 patients (9.3%).

Secondary prophylaxis

The reason for using anti-infectives was FN in 7 cycles (7.4%; 7 patients [3.1%]), CIN in 5 cycles (5.3%; 5 patients [2.2%]) or another reason in 82 cycles (87.2%; 39 patients [17.3%]). In the majority of cycles (71%) this other reason was the prophylaxis of infection. The route of anti-infectives was oral for 84 cycles (89.4%) in 39 patients (17.3%), and IV for 10 cycles (10.6%) in 10 patients (4.4%). The duration of anti-infectives use was 25.9 ± 56.1 days.

The reason for using anti-mycotics was FN in 4 cycles (9.3%; 2 patients [0.9%]), CIN in 4 cycles (9.3%; 4 patients [1.8%]) or another reason in 35 cycles (81.4%; 15 patients [6.7%]). In the majority of cycles (63%), prophylaxis of infection was the reason evoked for prescribing anti-mycotics. The route of anti-mycotics was oral in all 43 cycles (100.0%) in 18 patients (8.0%). The duration of anti-mycotics use was 20.8 ± 31.5 days.

The mean duration of hospitalization was 7.96 ± 7.88 days and the mean number of days spent in ICU was 2.65 ± 8.13 days. The reasons for hospitalisation were FN in 10 cycles (1.2%) in 10 patients (4.4%), CIN in 2 cycles (0.2%) in 2 patients (0.9%), infection in 3 cycles (0.4%) in 3 patients (1.3%), fever in 2 cycles (0.2%) in 2 patients (0.9%) and another reason in 10 cycles (1.2%) in 10 patients (4.4%).

7.5. Chemotherapy dose modifications following the first administration of Lonquex in primary prophylaxis

This analysis concerns the impact of Lonquex administration on CT dose modification following its administration in primary prophylaxis in chemotherapy cycle 1. It means that Lonquex was administered in chemotherapy cycle 1 and the impact on dose modification was assessed in chemotherapy cycle 2.

This cohort was constituted of 790 cycles in 790 patients.

Chemotherapy modifications

Number of patients and cycles in which chemotherapy omissions, delays and reductions were reported is shown in Table 32.

Table 32 Number of cycles and number of patients with chemotherapy omissions, delays and reductions (Efficacy population)

	Patients N=790
CT omission	
N (%)	0 (0.0)
Missing data: N (%)	2 (0.3)
CT delay	
N (%)	104 (13.2)
Missing data: N (%)	2 (0.3)
CT reduction	
N (%)	64 (8.1)
Missing data: N (%)	6 (0.8)

Biological treatment dose modifications

No BT was administered in 574 cycles (72.7%) in 574 patients (72.7%). A BT was administered in 216 cycles (27.3%) in 216 patients (27.3%). BT was not omitted in 215 cycles (27.2%) in 215 patients (27.2%). The BT dose was not reduced in 213 cycles (27.0%) in 213 patients (27.0%). The BT dose was reduced in 3 (0.4%) cycles in 3 patients (0.4%).

Overall CT and BT dose modifications and correlation with neutropenic events

Number of CT/BT omissions, delay and reductions have been recorded, however they can be associated with a smaller number of febrile neutropenia and neutropenia (Table 33), suggesting that there might be other reasons for observed dose modifications (e.g. logistics).

Table 33 Overall CT and BT dose modifications and correlation with neutropenic events (Efficacy population)

	Patients N=790
	n (%)
CT/BT delay, reduction or omission	159 (20.1)
- **Febrile neutropenia in these* cycles**	8 (5.0)
- **Neutropenia in these* cycles**	26 (16.4)
- **Grade III neutropenia in these* cycles**	9 (5.7)
- **Grade IV neutropenia in these* cycles**	9 (5.7)
Overlap of CT/BT dose modification and FN	8 (1.0)
Overlap of CT/BT dose modification and neutropenia	26 (3.3)
Overlap of CT/BT dose modification and grade III neutropenia	9 (1.1)
Overlap of CT/BT dose modification and grade IV neutropenia	9 (1.1)

**Cycles in which CT/BT dose omission, reduction or delay were reported*

7.6. Neutropenia and related events following the first administration of Lonquex in primary prophylaxis

In this analysis, the impact of Lonquex on neutropenia and related events following its administration in primary prophylaxis was evaluated in chemotherapy cycle 1.

Operationally, if neutropenia occurred in the cycle when Lonquex was administered, in eCRF it was recorded in the following cycle. E.g. if neutropenia occurred in cycle 1, it was recorded in cycle 2. However, in this report it is presented as neutropenia in cycle 1.

This cohort was constituted of 895 cycles in 895 patients.

The neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered can be found in Table 34.

Table 34 Neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered (Efficacy population)

	Patients N=895
	n (%)
Febrile neutropenia	16 (1.8)
Missing	6 (0.7)
Neutropenia	91 (10.2)
Missing	6 (0.7)
Grade III neutropenia	22 (2.5)
Grade IV neutropenia	45 (5.0)
Anti-infective	215 (24.0)
Missing	6 (0.7)
Anti-mycotic	56 (6.3)
Missing	6 (0.7)
Hospitalization	49 (5.5)
Missing	6 (0.7)
Blood transfusion	31 (3.5)
Missing	6 (0.7)
Death	5 (0.6)
Missing	6 (0.7)

The reason for using anti-infectives was FN in 8 cycles (3.7%; 8 patients [0.9%], CIN in 8 cycles (3.7%; 8 patients [0.9%]) or another reason in 198 cycles (92.5%; 198 patients [22.1%]). In the majority of cycles (75%) this other reason was the prophylaxis of infection. The route of administration was oral in 189 cycles (87.9%) in 189 patients

(21.1%) and IV in 26 cycles (12.1%) in 26 patients (2.9%). The duration of anti-infective use was 18.1 ± 26.3 days.

The reason for using anti-mycotics was CIN in 1 cycle (1.8%; 1 patient [0.1%]) or another reason in 55 cycles (98.2%; 55 patients [6.1%]). Prophylaxis of infection was the main other reason (84%) evoked for prescribing anti-mycotics. The route of anti-mycotics was oral in 54 cycles (96.4%) in 54 patients (6.0%), and IV in 2 cycles (3.6%) in 2 patients (0.2%). The duration of anti-mycotics use was 24.2 ± 26.9 days.

The mean duration of hospitalization was 9.59 ± 10.38 days and the mean number of days spent in ICU was 0.48 ± 2.1 days. The reasons for hospitalisation were FN in 8 cycles (0.9%) in 8 patients (0.9%), CIN in 2 cycles (0.2%) in 2 patients (0.2%), infection in 14 cycles (1.6%) in 14 patients (1.6%), fever in 1 cycle (0.1%) in 1 patient (0.1%) and another reason in 24 cycles (2.7%) in 24 patients (2.7%).

7.7. Chemotherapy dose modifications following the first administration of Lonquex in secondary prophylaxis

The impact of Lonquex administration on CT dose modification following the first administration of Lonquex in secondary prophylaxis was analysed. If Lonquex was administered in the chemotherapy cycle 2 in secondary prophylaxis, CT dose modifications were evaluated in chemotherapy cycle 3. In case that Lonquex administration in secondary prophylaxis started from cycle 3 or higher, it was ensured based on available data that no other G-CSF was administered in previous cycle(s). This includes information on FN or CIN and its timing prior to use of Lonquex in secondary prophylaxis in this study.

This cohort was constituted of 146 cycles in 146 patients.

Chemotherapy modifications

Number of patients and cycles in which chemotherapy omissions, delays and reductions were reported is shown in Table 35.

Table 35 Number of cycles and number of patients with chemotherapy omissions, delays and reductions (Efficacy population)

	Patients N=146
CT omission	
N (%)	1 (0.7)
Missing data: N (%)	0 (0.0)
CT delay	
N (%)	16 (11.0)
Missing data: N (%)	1 (0.7)
CT reduction	
N (%)	28 (19.2)
Missing data: N (%)	1 (0.7)

Biological treatment dose modifications

No BT was administered in 102 cycles (69.9%) in 102 patients (69.9%). A BT was administered in 44 cycles (30.1%) in 44 patients (30.1%).BT was not omitted in 44 cycles (30.1%) in 44 patients (30.1%). The BT dose was not reduced in 44 cycles (30.1%) in 44 patients (30.1%).

Overall CT and BT dose modifications and correlation with neutropenic events

Number of CT/BT omissions, delay and reductions have been recorded, however they can be associated with a smaller number of febrile neutropenia and neutropenia (Table

36), suggesting that there might be other reasons for observed dose modifications (e.g. logistics).

Table 36 Overall CT and BT dose modifications and correlation with neutropenic events (Efficacy population)

	Patients N=146
	n (%)
CT/BT delay, reduction or omission	41 (28.1)
- **Febrile neutropenia in these* cycles**	3 (7.3)
- **Neutropenia in these* cycles**	10 (24.4)
- **Grade III neutropenia in these* cycles**	3 (7.3)
- **Grade IV neutropenia in these* cycles**	5 (12.2)
Overlap of CT/BT dose modification and FN	3 (2.1)
Overlap of CT/BT dose modification and neutropenia	10 (6.8)
Overlap of CT/BT dose modification and grade III neutropenia	3 (2.1)
Overlap of CT/BT dose modification and grade IV neutropenia	5 (3.4)

**Cycles in which CT/BT dose omission, reduction or delay were reported*

7.8. Neutropenia and related events following the first administration of Lonquex in secondary prophylaxis

The impact of Lonquex administration on neutropenia and related events following its first administration in secondary prophylaxis was analysed. If Lonquex was administered in chemotherapy cycle 2 in secondary prophylaxis, the incidence of neutropenia and related events was analysed in that cycle. In case that Lonquex administration in secondary prophylaxis started from cycle 3 or higher, it was ensured based on available data that no other G-CSF was administered in previous cycle(s). This includes information on FN or CIN and its timing prior to use of Lonquex in secondary prophylaxis in this study.

Operationally, if neutropenia occurred in the cycle when Lonquex was administered, in eCRF it was recorded in the following cycle. E.g. if neutropenia occurred in cycle21, it was recorded in cycle 3. However, in this Report it is presented as neutropenia in cycle 2.

This cohort was constituted of 192 cycles in 192 patients.

The neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered can be found in Table 37.

Table 37 Neutropenic events, use of anti-infectives and anti-mycotics, hospitalizations, blood transfusions and deaths during cycles in which Lonquex was administered (Efficacy population)

	Patients N=192
	n (%)
Febrile neutropenia	2 (1.0)
Missing	4 (2.1)
Neutropenia	21 (10.9)
Missing	4 (2.1)
Grade III neutropenia	6 (3.1)
Grade IV neutropenia	7 (3.6)
Anti-infective	20 (10.4)
Missing	4 (2.1)
Anti-mycotic	9 (4.7)
Missing	4 (2.1)
Hospitalization	6 (3.1)
Missing	4 (2.1)
Blood transfusion	2 (1.0)
Missing	4 (2.1)
Death	0 (0.0)
Missing	4 (2.1)

The reason for using anti-infectives was another reason in all 20 cycles (100.0%; 20 patients [10.4%]). In the majority of cycles (60%) this other reason was the prophylaxis of infection. The route of administration was oral in 17 cycles (85.0%) in 17 patients (8.9%) and IV in 3 cycles (15.0%) in 3 patients (1.6%). The duration of anti-infective use was 20.9 ± 34.4 days.

The reason for using anti-mycotics was another reason in all 9 cycles (100.0%; 9 patients [4.7%]). Prophylaxis of infection was the main reason (67%) evoked for prescribing anti-mycotics. The route of anti-mycotics was oral in all 9 cycles (100.0%) in 9 patients (4.7%). The duration of anti-mycotics use was 35.8 ± 55.1 days.

The mean duration of hospitalization was 9.50 ± 5.75 days and no days were spent in ICU. The reasons for hospitalisation were FN in 1 cycle (0.5%) in 1 patient (0.5%), CIN in 0 cycle (0.0%) in 0 patient (0.0%), infection in 1 cycle (0.5%) in 1 patient (0.5%), fever in 1 cycle (0.5%) in 1 patient (0.5%) and another reason in 3 cycles (1.6%) in 3 patients (1.6%).

7.9. Efficacy conclusions

The most common dose modification in these studies was dose delay, followed by dose reduction. Numerically more chemotherapy dose reductions were reported when Lonquex was administered in secondary then when it was administered in primary prophylaxis. Chemotherapy dose reductions were reported in 14.4% of patients in primary prophylaxis and 20.7% of patients in secondary prophylaxis. For chemotherapy dose delays, the values were relatively similar in the two prophylaxis categories. Chemotherapy dose delays were recorded in 30.0% of patients when Lonquex was administered as primary prophylaxis, and 30.9% of patients when administered as secondary prophylaxis.

However in patients experiencing any kind of CT/BT dose modifications, this was less commonly associated with febrile neutropenia or severe neutropenia. A total of 40.3% of patients who received Lonquex in primary prophylaxis experienced any kind of CT/BT dose modification in at least one of the cycles. However, only 3.1% and 9.9% of these modifications were associated with febrile neutropenia or grade 3/4 neutropenia, respectively. In the group patients receiving Lonquex in secondary prophylaxis, 46.8% of them experienced some CT/BT dose modification throughout the study. However, only 9.1% and 19.3% of these modifications were associated with febrile neutropenia or grade 3/4 neutropenia, respectively.

In the cycle following the first Lonquex administration, CT dose delays were recorded in 13.2% of patients in PP and 11.0% of patients in SP. CT dose reductions were recorded in 8.1% of patients in PP and in 19.2% of patients in SP.

Although reported in a different way there is an alignment with interim data of another non-interventional study NADIR [11-13]. In NADIR study dose reductions were the most common dose modifications (22.4% of non-Hodgkin lymphomas, 17.0% of breast cancer patients and 5.8% of lung cancer patients receiving Lonquex either in PP or SP).

However, CT dose modifications were rarely associated with chemotherapy-induced neutropenia (0.7% of all cycles in non-Hodgkin lymphomas, 0.7% of all cycles in breats cancer patients and 1.6% of all cycles in lung cancer patients) [11-13].

In the phase III RCT in breast cancer patients receiving lipegfilgrastim as primary prophylaxis chemotherapy dose delays in CT cycle 2 were observed in 16.2% patients, with no dose omissions or reductions [9]. However, the difference between data obtained in this study and the Bondarenko et al. [1] study can be explained by much more controlled setting of RCTs compared to real-world studies, more homogeneous population than in RCTs, as well as different study population in terms of tumor types (breast cancer vs different solid tumors and haematological malignancies).

Febrile neutropenia was observed in 3.1% of patients receiving lipegfilgrastim as PP and in 8.0% of patients receiving it as SP. There were more patients affected by grade 3/4 neutropenia in SP (21.3%) than in PP (13.4%).

The incidences of grade 3/4 neutropenia in this study are lower than the ones observed in the NADIR study (interim analysis), in which grade 3/4 neutropenia has been observed in 37.1% of non-Hodgkin lymphoma patients, 29.4% of breast cancer patients and 33.1% of lung cancer patients receiving lipegfilgrastim either as primary or secondary prophylaxis. The incidence of grade 3 febrile neutropenia in the same study was 2% in non-Hodgkin lymphoma patients, 2.2% in breast cancer patients and 0.6% in lung cancer patients [11-13].

In RCT phase III study in breast cancer patients who were receiving lipegfilgrastim in primary prophylaxis no patient experienced febrile neutropenia in CT cycle 1. On the other hand sever neutropenia has been reported in 43.6% of patients in CT cycle 1, and in 50.0% of patients across all cycles [1].

The use of anti-infectives and anti-mycotics in this study was relatively high (30.5% and 10.0% of patients respectively). They were mainly used prophylactically.

Overall, lipegfilgrastim was effective in preventing incidence of febrile neutropenia and severe neutropenia in the real-world practice and the data were comparable with published data in similar population in similar study setting.

8. SAFETY RESULTS

8.1. Adverse events and serious adverse events

Overall, 1,575 AEs have been recorded in 561 out of the 1,313 patients (42.7%) of the safety population.

The frequencies of the AEs can be found in Table 38. The most frequent AEs in terms of % of affected patients were bone pain (6.17%), anemia (3.58%), pyrexia (3.88%) and myalgia (3.81%). All the other AEs had a frequency lower than 3%.

The causality relationship has been provided for all the AEs. The relationship was probable, possible, unlikely, not assessable and not related for 255 (16.2%), 164 (10.4%), 159 (10.1%), 11 (0.7%) and 986 (62.6%) AEs, respectively (Table 39).

Therefore a total of 589 ADRs (AEs considered probably, possibly, unlikely related to Lonquex + not assessable AEs) were reported by 284 patients (21.6%). They are listed in Table 40. The most frequent ADRs (>1%) in terms of % of affected patients were bone pain (5.86%), myalgia (3.43%), back pain (1.83%), arthralgia (1.68%) and pyrexia (1.14%). All the other ADRs had a frequency lower than 1%.

Overall, 249 SAEs have been recorded in 159 patients (12.1%). The frequencies of the SAEs can be found in Table 41. The most frequent SAEs (>1%) in terms of % of affected patients were FN (1.37%) and pyrexia (1.22%). All the other SAEs had a frequency lower than 1%.

The severity of SAEs can be found in Table 42. Their grade was 1, 2, 3, 4 and 5 for 23 (9.2%), 33 (13.3%), 125 (50.2%), 48 (19.3%) and 20 (8.0%) SAEs, respectively.

Overall, 65 SADRs (SAEs considered related to Lonquex) have been recorded in 42 patients (3.2%). The frequencies of the SAEs can be found in Table 43. No SADR had a frequency higher than 1% in terms of % of affected patients.

The severity of SADRs can be found in Table 44. Their grade was 1, 2, 3, 4 and 5 for 8 (12.3%), 10 (15.4%), 36 (55.4%), 7 (10.8%) and 4 (6.2%) SADRs, respectively.

Overall, 20 SAEs leading to death or defined as death occurred in 16 patients (1.22%). The death was considered related to Lonquex in 3 patients (0.23%). The events leading to death in the 16 patients were:

1) Septic shock
2) Disease progression + renal failure
3) General physical health deterioration
4) Death
5) Death
6) Death
7) Death

8) Febrile neutropenia (considered related to Lonquex)
9) Septic shock and aplastic anemia (considered related to Lonquex)
10) Hepatic failure
11) Disease progression and neoplasm progression
12) Complication associated with the device
13) Death with disease progression
14) Disease progression
15) Septic shock
16) Disease progression (considered related to Lonquex)

The identification of these 16 patients is provided in Table 45. Seven additional patients died, however this was not reported in association with AEs. The deaths were only reported within treatment cycle visits. The identifications of these patients is provided in Table 45.

As a consequence of AEs or SAEs, the study was discontinued in 72 patients (5.5%).

As a consequence of ADRs or SADRs, the study was discontinued in 30 patients (2.3%).

Table 38 Frequency of the adverse events coded in System Organ Classes and Preferred Terms with MedDRA (Safety population)

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
Blood and lymphatic system disorders	**Anaemia**	*51*	*3.2*	*47*	*3.58*
	Anaemia macrocytic	*2*	*0.1*	*1*	*0.08*
	Aplastic anaemia	*1*	*0.1*	*1*	*0.08*
	Febrile neutropenia	*20*	*1.3*	*20*	*1.52*
	Immune thrombocytopenic purpura	*1*	*0.1*	*1*	*0.08*
	Leukocytosis	*8*	*0.5*	*8*	*0.61*
	Leukopenia	*9*	*0.6*	*8*	*0.61*
	Lymph node pain	*1*	*0.1*	*1*	*0.08*
	Neutropenia	*43*	*2.7*	*33*	*2.51*
	Neutrophilia	*2*	*0.1*	*2*	*0.15*
	Normochromic normocytic anaemia	*1*	*0.1*	*1*	*0.08*
	Pancytopenia	*3*	*0.2*	*3*	*0.23*
	Thrombocytopenia	*50*	*3.2*	*31*	*2.36*
Cardiac disorders	**Angina pectoris**	*2*	*0.1*	*2*	*0.15*
	Angina unstable	*1*	*0.1*	*1*	*0.08*
	Atrial fibrillation	*4*	*0.3*	*4*	*0.30*
	Atrial flutter	*1*	*0.1*	*1*	*0.08*
	Cardiac failure	*1*	*0.1*	*1*	*0.08*
	Dyspnoea	*1*	*0.1*	*1*	*0.08*
	Extrasystoles	*1*	*0.1*	*1*	*0.08*
	Myocardial infarction	*1*	*0.1*	*1*	*0.08*
	Palpitations	*6*	*0.4*	*6*	*0.46*
	Sinus tachycardia	*1*	*0.1*	*1*	*0.08*
	Supraventricular tachycardia	*1*	*0.1*	*1*	*0.08*
	Tachycardia	*7*	*0.4*	*7*	*0.53*
	Ventricular hypokinesia	*1*	*0.1*	*1*	*0.08*
Congenital. familial and genetic disorders	**Aplasia**	*1*	*0.1*	*1*	*0.08*
Ear and labyrinth disorders	**Hypoacusis**	*1*	*0.1*	*1*	*0.08*
	Tinnitus	*3*	*0.2*	*1*	*0.08*
	Vertigo	*4*	*0.3*	*4*	*0.30*
Endocrine disorders	**Hyperthyroidism**	*1*	*0.1*	*1*	*0.08*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
Eye disorders	**Blepharitis**	*1*	*0.1*	*1*	*0.08*
	Dry eye	*4*	*0.3*	*4*	*0.30*
	Eye pain	*1*	*0.1*	*1*	*0.08*
	Lacrimation increased	*6*	*0.4*	*6*	*0.46*
	Ocular hyperaemia	*1*	*0.1*	*1*	*0.08*
	Photophobia	*2*	*0.1*	*2*	*0.15*
	Vision blurred	*1*	*0.1*	*1*	*0.08*
	Vitreous floaters	*1*	*0.1*	*1*	*0.08*
Gastrointestinal disorders	**Abdominal discomfort**	*3*	*0.2*	*3*	*0.23*
	Abdominal pain	*12*	*0.8*	*10*	*0.76*
	Abdominal pain upper	*11*	*0.7*	*8*	*0.61*
	Ascites	*1*	*0.1*	*1*	*0.08*
	Constipation	*4*	*0.3*	*4*	*0.30*
	Diarrhoea	*16*	*1.0*	*15*	*1.14*
	Diverticular perforation	*1*	*0.1*	*1*	*0.08*
	Dry mouth	*2*	*0.1*	*2*	*0.15*
	Duodenal perforation	*1*	*0.1*	*1*	*0.08*
	Dyspepsia	*16*	*1.0*	*14*	*1.07*
	Dysphagia	*6*	*0.4*	*6*	*0.46*
	Epigastralgia	*2*	*0.1*	*2*	*0.15*
	Epigastric discomfort	*4*	*0.3*	*4*	*0.30*
	Eructation	*1*	*0.1*	*1*	*0.08*
	Gastric disorder	*1*	*0.1*	*1*	*0.08*
	Gastric ulcer perforation	*1*	*0.1*	*1*	*0.08*
	Gastrointestinal haemorrhage	*1*	*0.1*	*1*	*0.08*
	Gastrointestinal pain	*1*	*0.1*	*1*	*0.08*
	Gastrooesophageal reflux disease	*2*	*0.1*	*2*	*0.15*
	Haemorrhoidal haemorrhage	*1*	*0.1*	*1*	*0.08*
	Haemorrhoids	*1*	*0.1*	*1*	*0.08*
	Ileus	*1*	*0.1*	*1*	*0.08*
	Ileus paralytic	*1*	*0.1*	*1*	*0.08*
	Intestinal perforation	*1*	*0.1*	*1*	*0.08*
	Melaena	*1*	*0.1*	*1*	*0.08*
	Nausea	*21*	*1.3*	*16*	*1.22*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Odynophagia	*1*	*0.1*	*1*	*0.08*
	Oesophagitis	*1*	*0.1*	*1*	*0.08*
	Oral pain	*1*	*0.1*	*1*	*0.08*
	Plicated tongue	*1*	*0.1*	*1*	*0.08*
	Proctalgia	*1*	*0.1*	*1*	*0.08*
	Rectal stenosis	*1*	*0.1*	*1*	*0.08*
	Salivary hypersecretion	*2*	*0.1*	*2*	*0.15*
	Stomatitis	*4*	*0.3*	*4*	*0.30*
	Teeth brittle	*1*	*0.1*	*1*	*0.08*
	Tongue discomfort	*1*	*0.1*	*1*	*0.08*
	Toothache	*4*	*0.3*	*4*	*0.30*
	Vomiting	*12*	*0.8*	*12*	*0.91*
General disorders and administration site conditions	**Asthenia**	*19*	*1.2*	*18*	*1.37*
	Chest pain	*14*	*0.9*	*11*	*0.84*
	Chills	*8*	*0.5*	*4*	*0.30*
	Complication associated with device	*1*	*0.1*	*1*	*0.08*
	Death	*6*	*0.4*	*6*	*0.46*
	Disease progression	*15*	*1.0*	*15*	*1.14*
	Drug intolerance	*1*	*0.1*	*1*	*0.08*
	Face oedema	*1*	*0.1*	*1*	*0.08*
	Fatigue	*13*	*0.8*	*6*	*0.46*
	Feeling hot	*2*	*0.1*	*1*	*0.08*
	General physical health deterioration	*7*	*0.4*	*5*	*0.38*
	Hyperpyrexia	*1*	*0.1*	*1*	*0.08*
	Hypothermia	*1*	*0.1*	*1*	*0.08*
	Influenza-like illness	*5*	*0.4*	*5*	*0.38*
	Injection site pain	*1*	*0.1*	*1*	*0.08*
	Injection site reaction	*1*	*0.1*	*1*	*0.08*
	Localised oedema	*1*	*0.1*	*1*	*0.08*
	Malaise	*13*	*0.8*	*13*	*0.99*
	Mucosal dryness	*1*	*0.1*	*1*	*0.08*
	Mucosal inflammation	*5*	*0.3*	*5*	*0.38*
	Oedema	*5*	*0.3*	*5*	*0.38*
	Oedema peripheral	*9*	*0.6*	*9*	*0.69*
	Pain	*22*	*1.4*	*19*	*1.45*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Peripheral swelling	*1*	*0.1*	*1*	*0.08*
	Pyrexia	*63*	*4.0*	*51*	*3.88*
	Secretion discharge	*1*	*0.1*	*1*	*0.08*
Hepatobiliary disorders	**Cholecystitis**	*1*	*0.1*	*1*	*0.08*
	Hepatic failure	*1*	*0.1*	*1*	*0.08*
	Hepatic function abnormal	*1*	*0.1*	*1*	*0.08*
	Hepatotoxicity	*1*	*0.1*	*1*	*0.08*
	Jaundice cholestatic	*1*	*0.1*	*1*	*0.08*
Immune system disorders	**Hypersensitivity**	*13*	*0.8*	*12*	*0.91*
	Seasonal allergy	*1*	*0.1*	*1*	*0.08*
Infections and infestations	**Anal abscess**	*1*	*0.1*	*1*	*0.08*
	Arteritis infective	*1*	*0.1*	*1*	*0.08*
	Bronchitis	*9*	*0.6*	*8*	*0.61*
	Campylobacter gastroenteritis	*1*	*0.1*	*1*	*0.08*
	Catheter site infection	*1*	*0.1*	*1*	*0.08*
	Conjunctivitis	*2*	*0.1*	*2*	*0.15*
	Cystitis	*8*	*0.5*	*8*	*0.61*
	Cytomegalovirus infection	*1*	*0.1*	*1*	*0.08*
	Deep vein thrombosis	*1*	*0.1*	*1*	*0.08*
	Device related infection	*1*	*0.1*	*1*	*0.08*
	Ear infection	*2*	*0.1*	*2*	*0.15*
	Erysipelas	*1*	*0.1*	*1*	*0.08*
	Escherichia urinary tract infection	*1*	*0.1*	*1*	*0.08*
	Folliculitis	*1*	*0.1*	*1*	*0.08*
	Fungal infection	*2*	*0.1*	*2*	*0.15*
	Fungal oesophagitis	*1*	*0.1*	*1*	*0.08*
	Gastroenteritis norovirus	*1*	*0.1*	*1*	*0.08*
	Gastroenteritis viral	*2*	*0.1*	*2*	*0.15*
	Genital herpes	*1*	*0.1*	*1*	*0.08*
	Genitourinary tract infection	*1*	*0.1*	*1*	*0.08*
	Herpes zoster	*4*	*0.3*	*4*	*0.30*
	Hordeolum	*1*	*0.1*	*1*	*0.08*
	Infection	*6*	*0.4*	*6*	*0.46*
	Infectious pleural effusion	*1*	*0.1*	*1*	*0.08*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Infective thrombosis	*1*	*0.1*	*1*	*0.08*
	Influenza	*1*	*0.1*	*1*	*0.08*
	Klebsiella infection	*1*	*0.1*	*1*	*0.08*
	Klebsiella sepsis	*1*	*0.1*	*1*	*0.08*
	Laryngitis	*1*	*0.1*	*1*	*0.08*
	Lip infection	*1*	*0.1*	*1*	*0.08*
	Localised infection	*3*	*0.2*	*3*	*0.23*
	Lung infection	*6*	*0.4*	*5*	*0.38*
	Mastitis	*3*	*0.2*	*3*	*0.23*
	Mucosal infection	*2*	*0.1*	*2*	*0.15*
	Oral candidiasis	*4*	*0.3*	*4*	*0.30*
	Otitis media	*1*	*0.1*	*1*	*0.08*
	Periodontitis	*1*	*0.1*	*1*	*0.08*
	Pharyngitis	*4*	*0.3*	*4*	*0.30*
	Pneumonia	*18*	*1.1*	*16*	*1.22*
	Pneumonia staphylococcal	*1*	*0.1*	*1*	*0.08*
	Postoperative wound infection	*4*	*0.3*	*4*	*0.30*
	Pseudomonas infection	*2*	*0.1*	*2*	*0.15*
	Rash pustular	*2*	*0.1*	*2*	*0.15*
	Respiratory tract infection	*11*	*0.7*	*11*	*0.84*
	Rhinitis	*2*	*0.1*	*2*	*0.15*
	Salmonellosis	*1*	*0.1*	*1*	*0.08*
	Sepsis	*5*	*0.3*	*5*	*0.38*
	Septic shock	*3*	*0.2*	*3*	*0.23*
	Sialoadenitis	*1*	*0.1*	*1*	*0.08*
	Sinusitis	*2*	*0.1*	*2*	*0.15*
	Skin infection	*2*	*0.1*	*2*	*0.15*
	Staphylococcal infection	*2*	*0.1*	*2*	*0.15*
	Streptococcal infection	*1*	*0.1*	*1*	*0.08*
	Tonsillitis	*2*	*0.1*	*2*	*0.15*
	Tooth infection	*1*	*0.1*	*1*	*0.08*
	Upper respiratory tract infection	*10*	*0.6*	*10*	*0.76*
	Urinary tract infection	*20*	*1.3*	*20*	*1.52*
	Vascular access site infection	*1*	*0.1*	*1*	*0.08*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Viraemia	*1*	*0.1*	*1*	*0.08*
	Viral infection	*1*	*0.1*	*1*	*0.08*
	Viral pharyngitis	*1*	*0.1*	*1*	*0.08*
	Viral upper respiratory tract infection	*9*	*0.6*	*9*	*0.69*
	Vulvovaginal candidiasis	*2*	*0.1*	*2*	*0.15*
	Wound infection	*2*	*0.1*	*2*	*0.15*
Injury. poisoning and procedural complications	**Femoral neck fracture**	*1*	*0.1*	*1*	*0.08*
	Incision site haemorrhage	*2*	*0.1*	*1*	*0.08*
	Infusion related reaction	*5*	*0.3*	*4*	*0.30*
	Overdose	*1*	*0.1*	*1*	*0.08*
	Radiation skin injury	*1*	*0.1*	*1*	*0.08*
	Stenosis of vesicourethral anastomosis	*1*	*0.1*	*1*	*0.08*
	Underdose	*1*	*0.1*	*1*	*0.08*
	Upper limb fracture	*1*	*0.1*	*1*	*0.08*
	Vertebral fracture	*1*	*0.1*	*1*	*0.08*
	Wound dehiscence	*1*	*0.1*	*1*	*0.08*
Investigations	**Alanine aminotransferase increased**	*1*	*0.1*	*1*	*0.08*
	Aspartate aminotransferase increased	*1*	*0.1*	*1*	*0.08*
	Blood creatinine increased	*3*	*0.2*	*2*	*0.15*
	Body temperature increased	*1*	*0.1*	*1*	*0.08*
	C-reactive protein increased	*2*	*0.1*	*2*	*0.15*
	Drug level changed	*1*	*0.1*	*1*	*0.08*
	Haemoglobin increased	*1*	*0.1*	*1*	*0.08*
	Liver function test increased	*1*	*0.1*	*1*	*0.08*
	Lymphocyte count decreased	*5*	*0.3*	*2*	*0.15*
	Neutrophil count decreased	*1*	*0.1*	*1*	*0.08*
	Platelet count decreased	*1*	*0.1*	*1*	*0.08*
	Weight decreased	*4*	*0.3*	*4*	*0.30*
	White blood cell count increased	*2*	*0.1*	*2*	*0.15*
Metabolism and nutrition disorders	**Decreased appetite**	*5*	*0.3*	*4*	*0.30*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Dehydration	*3*	*0.2*	*3*	*0.23*
	Diabetes mellitus	*1*	*0.1*	*1*	*0.08*
	Fluid retention	*1*	*0.1*	*1*	*0.08*
	Food aversion	*1*	*0.1*	*1*	*0.08*
	Hypercalcaemia	*2*	*0.1*	*2*	*0.15*
	Hyperglycaemia	*2*	*0.1*	*2*	*0.15*
	Hyperkalaemia	*1*	*0.1*	*1*	*0.08*
	Hypernatraemia	*2*	*0.1*	*1*	*0.08*
	Hypocalcaemia	*2*	*0.1*	*2*	*0.15*
	Hypokalaemia	*5*	*0.3*	*5*	*0.38*
	Hypomagnesaemia	*3*	*0.2*	*3*	*0.23*
	Malnutrition	*1*	*0.1*	*1*	*0.08*
	Starvation	*1*	*0.1*	*1*	*0.08*
Musculoskeletal and connective tissue disorders	**Arthralgia**	*36*	*2.3*	*27*	*2.06*
	Arthropathy	*1*	*0.1*	*1*	*0.08*
	Back pain	*37*	*2.3*	*26*	*1.98*
	Bone fistula	*1*	*0.1*	*1*	*0.08*
	Bone pain	*103*	*6.5*	*81*	*6.17*
	Bursitis	*1*	*0.1*	*1*	*0.08*
	Flank pain	*5*	*0.3*	*3*	*0.23*
	Joint swelling	*1*	*0.1*	*1*	*0.08*
	Muscle spasms	*1*	*0.1*	*1*	*0.08*
	Muscular weakness	*3*	*0.2*	*3*	*0.23*
	Musculoskeletal chest pain	*1*	*0.1*	*1*	*0.08*
	Musculoskeletal disorder	*4*	*0.3*	*4*	*0.30*
	Musculoskeletal pain	*13*	*0.8*	*7*	*0.53*
	Myalgia	*78*	*5.0*	*50*	*3.81*
	Neck pain	*7*	*0.4*	*4*	*0.30*
	Osteonecrosis of jaw	*1*	*0.1*	*1*	*0.08*
	Osteoporosis	*1*	*0.1*	*1*	*0.08*
	Pain in extremity	*4*	*0.3*	*4*	*0.30*
	Polyarthritis	*1*	*0.1*	*1*	*0.08*
	Soft tissue necrosis	*1*	*0.1*	*1*	*0.08*
	Spinal pain	*4*	*0.3*	*2*	*0.15*
Neoplasms benign. malignant and unspecified (incl cysts and polyps)	**Acute myeloid leukaemia**	*1*	*0.1*	*1*	*0.08*
	Infected neoplasm	*2*	*0.1*	*1*	*0.08*
	Lymphoma	*1*	*0.1*	*1*	*0.08*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Neoplasm progression	*3*	*0.2*	*3*	*0.23*
	Tumour inflammation	*1*	*0.1*	*1*	*0.08*
	Tumour pain	*1*	*0.1*	*1*	*0.08*
Nervous system disorders	**Akathisia**	*1*	*0.1*	*1*	*0.08*
	Aphonia	*1*	*0.1*	*1*	*0.08*
	Central pain syndrome	*1*	*0.1*	*1*	*0.08*
	Cerebrovascular accident	*2*	*0.1*	*2*	*0.15*
	Disturbance in attention	*1*	*0.1*	*1*	*0.08*
	Dizziness	*14*	*0.9*	*13*	*0.99*
	Dysgeusia	*2*	*0.1*	*2*	*0.15*
	Epilepsy	*1*	*0.1*	*1*	*0.08*
	Formication	*1*	*0.1*	*1*	*0.08*
	Headache	*26*	*1.6*	*19*	*1.44*
	Hemiparaesthesia	*1*	*0.1*	*1*	*0.08*
	Hyperaesthesia	*3*	*0.2*	*1*	*0.08*
	Hypoaesthesi	*1*	*0.1*	*1*	*0.08*
	Hypoaesthesia	*5*	*0.3*	*2*	*0.15*
	Migraine	*1*	*0.1*	*1*	*0.08*
	Neuropathy peripheral	*6*	*0.4*	*6*	*0.46*
	Paraesthesia	*2*	*0.1*	*2*	*0.15*
	Paresthesia	*2*	*0.1*	*2*	*0.15*
	Peripheral sensory neuropathy	*3*	*0.2*	*3*	*0.23*
	Polyneuropathy	*2*	*0.1*	*2*	*0.15*
	Presyncope	*2*	*0.1*	*2*	*0.15*
	Seizure	*1*	*0.1*	*1*	*0.08*
	Somnolence	*1*	*0.1*	*1*	*0.08*
	Syncope	*1*	*0.1*	*1*	*0.08*
	Tremor	*1*	*0.1*	*1*	*0.08*
Product issues	**Device issue**	*1*	*0.1*	*1*	*0.08*
Psychiatric disorders	**Agitation**	*1*	*0.1*	*1*	*0.08*
	Anxiety	*3*	*0.2*	*3*	*0.23*
	Conversion disorder	*1*	*0.1*	*1*	*0.08*
	Depression	*1*	*0.1*	*1*	*0.08*
	Depressive symptom	*1*	*0.1*	*1*	*0.08*
	Insomnia	*10*	*0.6*	*10*	*0.76*
	Sleep disorder	*2*	*0.1*	*2*	*0.15*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
Renal and urinary disorders	**Acute kidney injury**	*4*	*0.3*	*3*	*0.23*
	Anuria	*1*	*0.1*	*1*	*0.08*
	Bladder pain	*1*	*0.1*	*1*	*0.08*
	Chronic kidney disease	*1*	*0.1*	*1*	*0.08*
	Dysuria	*5*	*0.3*	*5*	*0.38*
	Haematuria	*3*	*0.2*	*2*	*0.15*
	Nocturia	*1*	*0.1*	*1*	*0.08*
	Oliguria	*1*	*0.1*	*1*	*0.08*
	Pollakiuria	*1*	*0.1*	*1*	*0.08*
	Renal colic	*1*	*0.1*	*1*	*0.08*
	Renal failure	*3*	*0.2*	*3*	*0.23*
	Renal haematoma	*1*	*0.1*	*1*	*0.08*
	Urinary tract pain	*1*	*0.1*	*1*	*0.08*
Reproductive system and breast disorders	**Breast pain**	*1*	*0.1*	*1*	*0.08*
	Breast swelling	*2*	*0.1*	*2*	*0.15*
	Menorrhagia	*1*	*0.1*	*1*	*0.08*
	Menstruation irregular	*2*	*0.1*	*2*	*0.15*
	Pelvic pain	*4*	*0.3*	*3*	*0.23*
	Testicular swelling	*1*	*0.1*	*1*	*0.08*
	Vaginal haemorrhage	*2*	*0.1*	*1*	*0.08*
	Vulvovaginal dryness	*1*	*0.1*	*1*	*0.08*
Respiratory. thoracic and mediastinal disorders	**Asthma**	*1*	*0.1*	*1*	*0.08*
	Bronchitis chronic	*1*	*0.1*	*1*	*0.08*
	Cough	*29*	*1.8*	*26*	*1.98*
	Dysphonia	*2*	*0.1*	*2*	*0.15*
	Dyspnoea	*37*	*2.3*	*34*	*2.59*
	Dyspnoea exertional	*2*	*0.1*	*2*	*0.15*
	Epistaxis	*14*	*0.9*	*14*	*1.07*
	Haemothorax	*1*	*0.1*	*1*	*0.08*
	Oropharyngeal pain	*6*	*0.4*	*5*	*0.38*
	Pneumomediastinum	*1*	*0.1*	*1*	*0.08*
	Pneumonia	*1*	*0.1*	*1*	*0.08*
	Pneumonitis	*8*	*0.5*	*7*	*0.53*
	Pneumothorax	*1*	*0.1*	*1*	*0.08*
	Pulmonary embolism	*4*	*0.3*	*4*	*0.30*
	Pulmonary oedema	*1*	*0.1*	*1*	*0.08*
	Pulmonary toxicity	*1*	*0.1*	*1*	*0.08*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Respiratory distress	*1*	*0.1*	*1*	*0.08*
	Throat irritation	*1*	*0.1*	*1*	*0.08*
Skin and subcutaneous tissue disorders	**Acne**	*4*	*0.3*	*1*	*0.08*
	Actinic keratosis	*1*	*0.1*	*1*	*0.08*
	Alopecia	*3*	*0.2*	*3*	*0.23*
	Dermatitis acneiform	*2*	*0.1*	*1*	*0.08*
	Dermatitis allergic	*1*	*0.1*	*1*	*0.08*
	Dermatitis bullous	*1*	*0.1*	*1*	*0.08*
	Drug eruption	*1*	*0.1*	*1*	*0.08*
	Dry skin	*4*	*0.3*	*4*	*0.30*
	Eczema	*2*	*0.1*	*2*	*0.15*
	Erythema	*7*	*0.5*	*7*	*0.54*
	Erythema multiforme	*1*	*0.1*	*1*	*0.08*
	Exfoliative rash	*1*	*0.1*	*1*	*0.08*
	Nail discolouration	*3*	*0.2*	*3*	*0.23*
	Pruritus	*5*	*0.3*	*5*	*0.38*
	Purpura	*1*	*0.1*	*1*	*0.08*
	Rash	*14*	*0.9*	*11*	*0.84*
	Rash generalised	*1*	*0.1*	*1*	*0.08*
	Rash maculo-papular	*6*	*0.4*	*4*	*0.30*
	Rash papular	*1*	*0.1*	*1*	*0.08*
	Rash pruritic	*2*	*0.1*	*2*	*0.15*
	Rash pustular	*2*	*0.1*	*2*	*0.15*
	Scar pain	*1*	*0.1*	*1*	*0.08*
	Skin dystrophy	*1*	*0.1*	*1*	*0.08*
	Skin exfoliation	*1*	*0.1*	*1*	*0.08*
	Skin hyperpigmentation	*1*	*0.1*	*1*	*0.08*
	Skin toxicity	*1*	*0.1*	*1*	*0.08*
	Urticaria	*2*	*0.1*	*2*	*0.15*
Surgical and medical procedures	**Tooth extraction**	*1*	*0.1*	*1*	*0.08*
	Uterine dilation and curettage	*1*	*0.1*	*1*	*0.08*
Vascular disorders	**Deep vein thrombosis**	*10*	*0.6*	*10*	*0.76*
	Embolism	*2*	*0.1*	*2*	*0.15*
	Flushing	*3*	*0.2*	*2*	*0.15*
	Haematoma	*2*	*0.1*	*2*	*0.15*
	Hot flush	*9*	*0.6*	*9*	*0.69*

SOC Term	PT Term	*Number of AE*	*% of AE*	*Number of patient*	*% of patient*
	Hypertension	*7*	*0.4*	*6*	*0.46*
	Hypotension	*14*	*0.9*	*13*	*0.99*
	Subclavian vein thrombosis	*1*	*0.1*	*1*	*0.08*
	Thrombophlebitis	*1*	*0.1*	*1*	*0.08*
	Thrombophlebitis superficial	*4*	*0.3*	*3*	*0.23*
	Varicose vein	*1*	*0.1*	*1*	*0.08*
	Venous thrombosis limb	*1*	*0.1*	*1*	*0.08*
	Total	*1575*	*100.0*	*561*	*42.7*

Table 39 Adverse events: causality relationship to Lonquex (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Probable	*255*	*16.2*	*16.2*	*16.2*
	Possible	*164*	*10.4*	*10.4*	*26.6*
	Unlikely	*159*	*10.1*	*10.1*	*36.7*
	Not assessable	*11*	*.7*	*.7*	*37.4*
	Not related	*986*	*62.6*	*62.6*	*100.0*
	Total	*1575*	*100.0*	*100.0*	

Table 40 Frequency of the ADRs coded in System Organ Classes and Preferred Terms with MedDRA (Safety population)

SOC Term	PT Term	Number of ADR	% of ADR	Number of patient	% of patient
Blood and lymphatic system disorders	Anaemia	*10*	*1.7*	*10*	*0.76*
	Aplastic anaemia	*1*	*0.2*	*1*	*0.08*
	Febrile neutropenia	*4*	*0.7*	*4*	*0.30*
	Immune thrombocytopenic purpura	*1*	*0.2*	*1*	*0.08*
	Leukocytosis	*6*	*1.0*	*6*	*0.46*
	Leukopenia	*2*	*0.3*	*2*	*0.15*
	Lymph node pain	*1*	*0.2*	*1*	*0.08*
	Neutropenia	*5*	*0.8*	*5*	*0.38*
	Neutrophilia	*2*	*0.3*	*2*	*0.15*
	Normochromic normocytic anaemia	*1*	*0.2*	*1*	*0.08*
	Thrombocytopenia	*12*	*2.0*	*8*	*0.61*
Cardiac disorders	Angina unstable	*1*	*0.2*	*1*	*0.08*
	Atrial fibrillation	*2*	*0.3*	*2*	*0.15*
	Atrial flutter	*1*	*0.2*	*1*	*0.08*
	Dyspnoea	*1*	*0.2*	*1*	*0.08*
	Palpitations	*5*	*0.8*	*5*	*0.38*
	Tachycardia	*1*	*0.2*	*1*	*0.08*
Congenital. familial and genetic disorders	Aplasia	*1*	*0.2*	*1*	*0.08*
Ear and labyrinth disorders	Hypoacusis	*1*	*0.2*	*1*	*0.08*
	Vertigo	*1*	*0.2*	*1*	*0.08*
Eye disorders	Eye pain	*1*	*0.2*	*1*	*0.08*
	Lacrimation increased	*2*	*0.3*	*2*	*0.15*
	Vitreous floaters	*1*	*0.2*	*1*	*0.08*
Gastrointestinal disorders	Abdominal discomfort	*1*	*0.2*	*1*	*0.08*
	Abdominal pain	*1*	*0.2*	*1*	*0.08*
	Abdominal pain upper	*5*	*0.8*	*3*	*0.23*
	Diarrhoea	*5*	*0.8*	*4*	*0.30*
	Dyspepsia	*1*	*0.2*	*1*	*0.08*
	Dysphagia	*1*	*0.2*	*1*	*0.08*
	Gastrointestinal pain	*1*	*0.2*	*1*	*0.08*
	Nausea	*7*	*1.2*	*7*	*0.53*
	Plicated tongue	*1*	*0.2*	*1*	*0.08*

	Stomatitis	***1***	***0.2***	***1***	***0.08***
	Toothache	***1***	***0.2***	***1***	***0.08***
	Vomiting	***4***	***0.7***	***4***	***0.30***
General disorders and administration site conditions	**Asthenia**	***8***	***1.4***	***8***	***0.61***
	Chest pain	***7***	***1.2***	***7***	***0.53***
	Chills	***6***	***1.0***	***3***	***0.23***
	Disease progression	***1***	***0.2***	***1***	***0.08***
	Face oedema	***1***	***0.2***	***1***	***0.08***
	Fatigue	***7***	***1.2***	***4***	***0.30***
	Influenza-like illness	***2***	***0.3***	***2***	***0.15***
	Injection site pain	***1***	***0.2***	***1***	***0.08***
	Localised oedema	***1***	***0.2***	***1***	***0.08***
	Malaise	***9***	***1.5***	***9***	***0.69***
	Oedema	***4***	***0.7***	***4***	***0.30***
	Oedema peripheral	***2***	***0.3***	***2***	***0.15***
	Pain	***19***	***3.2***	***16***	***1.22***
	Pyrexia	***17***	***2.9***	***15***	***1.14***
Hepatobiliary disorders	**Cholecystitis**	***1***	***0.2***	***1***	***0.08***
	Hepatic function abnormal	***1***	***0.2***	***1***	***0.08***
	Jaundice cholestatic	***1***	***0.2***	***1***	***0.08***
Immune system disorders	**Hypersensitivity**	***5***	***0.8***	***5***	***0.38***
Infections and infestations	**Campylobacter gastroenteritis**	***1***	***0.2***	***1***	***0.08***
	Device related infection	***1***	***0.2***	***1***	***0.08***
	Folliculitis	***1***	***0.2***	***1***	***0.08***
	Fungal infection	***1***	***0.2***	***1***	***0.08***
	Herpes zoster	***1***	***0.2***	***1***	***0.08***
	Infection	***1***	***0.2***	***1***	***0.08***
	Infective thrombosis	***1***	***0.2***	***1***	***0.08***
	Klebsiella infection	***1***	***0.2***	***1***	***0.08***
	Laryngitis	***1***	***0.2***	***1***	***0.08***
	Lip infection	***1***	***0.2***	***1***	***0.08***
	Oral candidiasis	***1***	***0.2***	***1***	***0.08***
	Otitis media	***1***	***0.2***	***1***	***0.08***
	Periodontitis	***1***	***0.2***	***1***	***0.08***
	Pharyngitis	***1***	***0.2***	***1***	***0.08***
	Pneumonia	***1***	***0.2***	***1***	***0.08***
	Postoperative wound infection	***1***	***0.2***	***1***	***0.08***

	Rash pustular	***1***	***0.2***	***1***	***0.08***
	Sepsis	***2***	***0.3***	***2***	***0.15***
	Septic shock	***1***	***0.2***	***1***	***0.08***
	Sialoadenitis	***1***	***0.2***	***1***	***0.08***
	Upper respiratory tract infection	***2***	***0.3***	***2***	***0.15***
	Urinary tract infection	***3***	***0.5***	***3***	***0.23***
	Vascular access site infection	***1***	***0.2***	***1***	***0.08***
	Viral infection	***1***	***0.2***	***1***	***0.08***
	Viral pharyngitis	***1***	***0.2***	***1***	***0.08***
	Viral upper respiratory tract infection	***1***	***0.2***	***1***	***0.08***
	Wound infection	***1***	***0.2***	***1***	***0.08***
Injury. poisoning and procedural complications	**Infusion related reaction**	***2***	***0.3***	***1***	***0.08***
	Overdose	***1***	***0.2***	***1***	***0.08***
	Radiation skin injury	***1***	***0.2***	***1***	***0.08***
Investigations	**Body temperature increased**	***1***	***0.2***	***1***	***0.08***
	Platelet count decreased	***1***	***0.2***	***1***	***0.08***
	Weight decreased	***1***	***0.2***	***1***	***0.08***
	White blood cell count increased	***1***	***0.2***	***1***	***0.08***
Metabolism and nutrition disorders	**Fluid retention**	***1***	***0.2***	***1***	***0.08***
	Hypernatraemia	***1***	***0.2***	***1***	***0.08***
	Hypocalcaemia	***1***	***0.2***	***1***	***0.08***
	Hypomagnesaemia	***1***	***0.2***	***1***	***0.08***
Musculoskeletal and connective tissue disorders	**Arthralgia**	***31***	***5.3***	***22***	***1.68***
	Arthropathy	***1***	***0.2***	***1***	***0.08***
	Back pain	***33***	***5.6***	***24***	***1.83***
	Bone pain	***99***	***16.8***	***77***	***5.86***
	Flank pain	***2***	***0.3***	***2***	***0.15***
	Muscular weakness	***3***	***0.5***	***3***	***0.23***
	Musculoskeletal chest pain	***1***	***0.2***	***1***	***0.08***
	Musculoskeletal disorder	***4***	***0.7***	***4***	***0.30***
	Musculoskeletal pain	***12***	***2.0***	***6***	***0.46***
	Myalgia	***71***	***12.1***	***45***	***3.43***
	Neck pain	***6***	***1.0***	***3***	***0.23***
	Osteoporosis	***1***	***0.2***	***1***	***0.08***

	Pain in extremity	***3***	***0.5***	***3***	***0.23***
	Soft tissue necrosis	***1***	***0.2***	***1***	***0.08***
Nervous system disorders	**Aphonia**	***1***	***0.2***	***1***	***0.08***
	Dizziness	***6***	***1.0***	***6***	***0.46***
	Formication	***1***	***0.2***	***1***	***0.08***
	Headache	***14***	***2.4***	***9***	***0.69***
	Hyperaesthesia	***3***	***0.5***	***1***	***0.08***
	Hypoaesthesia	***1***	***0.2***	***1***	***0.08***
	Neuropathy peripheral	***2***	***0.3***	***2***	***0.15***
	Presyncope	***1***	***0.2***	***1***	***0.08***
	Somnolence	***1***	***0.2***	***1***	***0.08***
Psychiatric disorders	**Anxiety**	***1***	***0.2***	***1***	***0.08***
	Depressive symptom	***1***	***0.2***	***1***	***0.08***
	Insomnia	***2***	***0.3***	***2***	***0.15***
Renal and urinary disorders	**Dysuria**	***2***	***0.3***	***2***	***0.15***
	Haematuria	***1***	***0.2***	***1***	***0.08***
	Nocturia	***1***	***0.2***	***1***	***0.08***
Reproductive system and breast disorders	**Breast pain**	***1***	***0.2***	***1***	***0.08***
	Pelvic pain	***4***	***0.7***	***3***	***0.23***
	Vulvovaginal dryness	***1***	***0.2***	***1***	***0.08***
Respiratory. thoracic and mediastinal disorders	**Cough**	***5***	***0.8***	***5***	***0.38***
	Dysphonia	***2***	***0.3***	***2***	***0.15***
	Dyspnoea	***10***	***1.7***	***8***	***0.61***
	Epistaxis	***2***	***0.3***	***2***	***0.15***
	Oropharyngeal pain	***3***	***0.5***	***2***	***0.15***
	Throat irritation	***1***	***0.2***	***1***	***0.08***
Skin and subcutaneous tissue disorders	**Actinic keratosis**	***1***	***0.2***	***1***	***0.08***
	Dermatitis acneiform	***1***	***0.2***	***1***	***0.08***
	Exfoliative rash	***1***	***0.2***	***1***	***0.08***
	Pruritus	***1***	***0.2***	***1***	***0.08***
	Rash	***3***	***0.5***	***3***	***0.23***
	Rash maculo-papular	***2***	***0.3***	***2***	***0.15***
	Rash papular	***1***	***0.2***	***1***	***0.08***
	Rash pustular	***2***	***0.3***	***2***	***0.15***
	Skin exfoliation	***1***	***0.2***	***1***	***0.08***
	Skin toxicity	***1***	***0.2***	***1***	***0.08***
	Urticaria	***1***	***0.2***	***1***	***0.08***
Vascular disorders	**Deep vein thrombosis**	***3***	***0.5***	***3***	***0.23***
	Embolism	***1***	***0.2***	***1***	***0.08***

	Flushing	***1***	***0.2***	***1***	***0.08***
	Hot flush	***3***	***0.5***	***3***	***0.23***
	Hypotension	***1***	***0.2***	***1***	***0.08***
	Subclavian vein thrombosis	***1***	***0.2***	***1***	***0.08***
	Thrombophlebitis	***1***	***0.2***	***1***	***0.08***
	Total	***589***	***100.0***	***284***	***21.6***

Table 41 Frequency of the SAEs coded in System Organ Classes and Preferred Terms with MedDRA (Safety population)

SOC Term	PT Term	Number of SAE	% of SAE	Number of patient	% of patient
Blood and lymphatic system disorders	**Anaemia**	*6*	*2.4*	*6*	*0.46*
	Aplastic anaemia	*1*	*0.4*	*1*	*0.08*
	Febrile neutropenia	*18*	*7.2*	*18*	*1.37*
	Leukopenia	*1*	*0.4*	*1*	*0.08*
	Neutropenia	*12*	*4.8*	*10*	*0.76*
	Pancytopenia	*2*	*0.8*	*2*	*0.15*
	Thrombocytopenia	*10*	*4.0*	*8*	*0.61*
Cardiac disorders	**Angina unstable**	*1*	*0.4*	*1*	*0.08*
	Atrial fibrillation	*3*	*1.2*	*3*	*0.23*
	Atrial flutter	*1*	*0.4*	*1*	*0.08*
	Dyspnoea	*1*	*0.4*	*1*	*0.08*
	Myocardial infarction	*1*	*0.4*	*1*	*0.08*
Congenital. familial and genetic disorders	**Aplasia**	*1*	*0.4*	*1*	*0.08*
Ear and labyrinth disorders	**Vertigo**	*1*	*0.4*	*1*	*0.08*
Eye disorders	**Photophobia**	*1*	*0.4*	*1*	*0.08*
Gastrointestinal disorders	**Abdominal discomfort**	*1*	*0.4*	*1*	*0.08*
	Abdominal pain upper	*1*	*0.4*	*1*	*0.08*
	Diarrhoea	*4*	*1.6*	*4*	*0.30*
	Diverticular perforation	*1*	*0.4*	*1*	*0.08*
	Duodenal perforation	*1*	*0.4*	*1*	*0.08*
	Dyspepsia	*1*	*0.4*	*1*	*0.08*
	Gastric ulcer perforation	*1*	*0.4*	*1*	*0.08*
	Gastrointestinal haemorrhage	*1*	*0.4*	*1*	*0.08*
	Haemorrhoidal haemorrhage	*1*	*0.4*	*1*	*0.08*
	Ileus	*1*	*0.4*	*1*	*0.08*
	Ileus paralytic	*1*	*0.4*	*1*	*0.08*
	Intestinal perforation	*1*	*0.4*	*1*	*0.08*
	Nausea	*6*	*2.4*	*4*	*0.30*
	Rectal stenosis	*1*	*0.4*	*1*	*0.08*
	Stomatitis	*1*	*0.4*	*1*	*0.08*
	Toothache	*1*	*0.4*	*1*	*0.08*
	Vomiting	*4*	*1.6*	*4*	*0.30*

General disorders and administration site conditions	**Asthenia**	***6***	***2.4***	***6***	***0.46***
	Chest pain	***3***	***1.2***	***3***	***0.23***
	Complication associated with device	***1***	***0.4***	***1***	***0.08***
	Death	***5***	***2.0***	***5***	***0.38***
	Disease progression	***10***	***4.0***	***10***	***0.76***
	Drug intolerance	***1***	***0.4***	***1***	***0.08***
	General physical health deterioration	***3***	***1.2***	***3***	***0.23***
	Malaise	***3***	***1.2***	***3***	***0.23***
	Oedema peripheral	***1***	***0.4***	***1***	***0.08***
	Pain	***1***	***0.4***	***1***	***0.08***
	Pyrexia	***19***	***7.6***	***16***	***1.22***
Hepatobiliary disorders	**Cholecystitis**	***1***	***0.4***	***1***	***0.08***
	Hepatic failure	***1***	***0.4***	***1***	***0.08***
Immune system disorders	**Hypersensitivity**	***2***	***0.8***	***2***	***0.15***
Infections and infestations	**Bronchitis**	***2***	***0.8***	***2***	***0.15***
	Campylobacter gastroenteritis	***1***	***0.4***	***1***	***0.08***
	Cytomegalovirus infection	***1***	***0.4***	***1***	***0.08***
	Fungal oesophagitis	***1***	***0.4***	***1***	***0.08***
	Gastroenteritis norovirus	***1***	***0.4***	***1***	***0.08***
	Infection	***3***	***1.2***	***3***	***0.23***
	Infectious pleural effusion	***1***	***0.4***	***1***	***0.08***
	Klebsiella infection	***1***	***0.4***	***1***	***0.08***
	Klebsiella sepsis	***1***	***0.4***	***1***	***0.08***
	Lung infection	***3***	***1.2***	***2***	***0.15***
	Pharyngitis	***1***	***0.4***	***1***	***0.08***
	Pneumonia	***12***	***4.8***	***11***	***0.84***
	Postoperative wound infection	***2***	***0.8***	***2***	***0.15***
	Respiratory tract infection	***4***	***1.6***	***4***	***0.30***
	Sepsis	***4***	***1.6***	***4***	***0.30***
	Septic shock	***3***	***1.2***	***3***	***0.23***
	Upper respiratory tract infection	***2***	***0.8***	***2***	***0.15***
	Urinary tract infection	***3***	***1.2***	***3***	***0.23***
	Wound infection	***1***	***0.4***	***1***	***0.08***

Injury. poisoning and procedural complications	**Femoral neck fracture**	***1***	***0.4***	***1***	***0.08***
	Incision site haemorrhage	***2***	***0.8***	***1***	***0.08***
	Infusion related reaction	***1***	***0.4***	***1***	***0.08***
	Radiation skin injury	***1***	***0.4***	***1***	***0.08***
	Stenosis of vesicourethral anastomosis	***1***	***0.4***	***1***	***0.08***
	Vertebral fracture	***1***	***0.4***	***1***	***0.08***
Investigations	**Drug level changed**	***1***	***0.4***	***1***	***0.08***
	Haemoglobin increased	***1***	***0.4***	***1***	***0.08***
	Lymphocyte count decreased	***1***	***0.4***	***1***	***0.08***
Metabolism and nutrition disorders	**Dehydration**	***2***	***0.8***	***2***	***0.15***
	Hypocalcaemia	***1***	***0.4***	***1***	***0.08***
	Hypomagnesaemia	***1***	***0.4***	***1***	***0.08***
	Malnutrition	***1***	***0.4***	***1***	***0.08***
	Starvation	***1***	***0.4***	***1***	***0.08***
Musculoskeletal and connective tissue disorders	**Bone pain**	***4***	***1.6***	***4***	***0.30***
	Osteonecrosis of jaw	***1***	***0.4***	***1***	***0.08***
Neoplasms benign. malignant and unspecified (incl cysts and polyps)	**Acute myeloid leukaemia**	***1***	***0.4***	***1***	***0.08***
	Lymphoma	***1***	***0.4***	***1***	***0.08***
	Neoplasm progression	***1***	***0.4***	***1***	***0.08***
Nervous system disorders	**Cerebrovascular accident**	***2***	***0.8***	***2***	***0.15***
	Dizziness	***2***	***0.8***	***2***	***0.15***
	Headache	***1***	***0.4***	***1***	***0.08***
Product issues	**Device issue**	***1***	***0.4***	***1***	***0.08***
Renal and urinary disorders	**Acute kidney injury**	***2***	***0.8***	***2***	***0.15***
	Chronic kidney disease	***1***	***0.4***	***1***	***0.08***
	Dysuria	***1***	***0.4***	***1***	***0.08***
	Haematuria	***3***	***1.2***	***2***	***0.15***
	Renal failure	***2***	***0.8***	***2***	***0.15***
Respiratory. thoracic and mediastinal disorders	**Dyspnoea**	***1***	***0.4***	***1***	***0.08***
	Haemothorax	***1***	***0.4***	***1***	***0.08***
	Oropharyngeal pain	***1***	***0.4***	***1***	***0.08***
	Pneumonitis	***7***	***2.8***	***7***	***0.53***
	Pneumothorax	***1***	***0.4***	***1***	***0.08***
	Pulmonary embolism	***3***	***1.2***	***3***	***0.23***
	Pulmonary toxicity	***1***	***0.4***	***1***	***0.08***
Surgical and medical procedures	**Uterine dilation and curettage**	***1***	***0.4***	***1***	***0.08***

Vascular disorders	**Deep vein thrombosis**	***1***	***0.4***	***1***	***0.08***
	Embolism	***1***	***0.4***	***1***	***0.08***
	Total	***249***	***100.0***	***159***	***12.1***

Table 42 Severity of the SAEs (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	**1**	***23***	***9.2***	***9.2***	***9.2***
	2	***33***	***13.3***	***13.3***	***22.5***
	3	***125***	***50.2***	***50.2***	***72.7***
	4	***48***	***19.3***	***19.3***	***92.0***
	5	***20***	***8.0***	***8.0***	***100.0***
	Total	***249***	***100.0***	***100.0***	

Table 43 Frequency of the SADRs coded in System Organ Classes and Preferred Terms with MedDRA (Safety population)

SOC Term	PT Term	Number of SADR	% of SADR	Number of patient	% of patient
Blood and lymphatic system disorders	Anaemia	1	1.5	1	0.08
	Aplastic anaemia	1	1.5	1	0.08
	Febrile neutropenia	4	6.2	4	0.30
	Neutropenia	2	3.1	2	0.15
	Thrombocytopenia	2	3.1	2	0.15
Cardiac disorders	Angina unstable	1	1.5	1	0.08
	Atrial fibrillation	2	3.1	2	0.15
	Atrial flutter	1	1.5	1	0.08
	Dyspnoea	1	1.5	1	0.08
Congenital. familial and genetic disorders	Aplasia	1	1.5	1	0.08
Ear and labyrinth disorders	Vertigo	1	1.5	1	0.08
Gastrointestinal disorders	Abdominal pain upper	1	1.5	1	0.08
	Nausea	2	3.1	2	0.15
	Stomatitis	1	1.5	1	0.08
	Toothache	1	1.5	1	0.08
General disorders and administration site conditions	Asthenia	4	6.2	4	0.30
	Chest pain	3	4.6	3	0.23
	Disease progression	1	1.5	1	0.08
	Malaise	3	4.6	3	0.23
	Pain	1	1.5	1	0.08
	Pyrexia	4	6.2	4	0.30
Hepatobiliary disorders	Cholecystitis	1	1.5	1	0.08
Immune system disorders	Hypersensitivity	2	3.1	2	0.15
Infections and infestations	Campylobacter gastroenteritis	1	1.5	1	0.08
	Klebsiella infection	1	1.5	1	0.08
	Pharyngitis	1	1.5	1	0.08
	Pneumonia	1	1.5	1	0.08
	Postoperative wound infection	1	1.5	1	0.08
	Sepsis	2	3.1	2	0.15
	Septic shock	1	1.5	1	0.08
	Wound infection	1	1.5	1	0.08

Injury. poisoning and procedural complications	**Radiation skin injury**	***1***	***1.5***	***1***	***0.08***
Metabolism and nutrition disorders	**Hypocalcaemia**	***1***	***1.5***	***1***	***0.08***
	Hypomagnesaemia	***1***	***1.5***	***1***	***0.08***
Musculoskeletal and connective tissue disorders	**Bone pain**	***4***	***6.2***	***4***	***0.30***
Nervous system disorders	**Dizziness**	***2***	***3.1***	***2***	***0.15***
	Headache	***1***	***1.5***	***1***	***0.08***
Renal and urinary disorders	**Dysuria**	***1***	***1.5***	***1***	***0.08***
	Haematuria	***1***	***1.5***	***1***	***0.08***
Respiratory. thoracic and mediastinal disorders	**Dyspnoea**	***1***	***1.5***	***1***	***0.08***
	Oropharyngeal pain	***1***	***1.5***	***1***	***0.08***
Vascular disorders	**Embolism**	***1***	***1.5***	***1***	***0.08***
	Total	***65***	***100.0***	***42***	***3.2***

Table 44 Severity of the SADRs (Safety population)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	*8*	*12.3*	*12.3*	*12.3*
	2	*10*	*15.4*	*15.4*	*27.7*
	3	*36*	*55.4*	*55.4*	*83.1*
	4	*7*	*10.8*	*10.8*	*93.8*
	5	*4*	*6.2*	*6.2*	*100.0*
	Total	*65*	*100.0*	*100.0*	

Table 45 Identification of patients dying during the study (Safety population)

Patient number	Patient dying during cycles	Deaths reported as AEs
AT-02-002	YES	NO
AT-09-048	YES	NO
BE-12-003	YES	YES
BE-16-002	YES	YES
BE-16-017	NO	YES
CZ-06-005	YES	NO
ITL-04-001	NO	YES
ITL-06-020	YES	NO
ITL-15-009	NO	YES
ITL-19-022	YES	YES
ITP-01-004	YES	YES
ITP-05-006	NO	YES
ITP-14-008	YES	YES
ITP-25-006	YES	YES
NL-02-004	YES	NO
NL-04-004	YES	YES
NL-04-005	YES	YES
PL-05-008	YES	YES
PL-11-015	YES	YES
PL-13-006	YES	YES
SK-002-003	YES	NO
SK-013-006	YES	NO
SK-023-002	YES	YES

8.2. Pregnancies and special situations

No pregnancies were reported.

The following special situations were reported:

1) Overdose in 1 patient in Italy. This patient was kept in both the safety and the efficacy populations.
2) Minor errors of prescription in 3 patients (1 in the Netherlands, 1 in Italy and 1 in Belgium). These three patients were kept in both the safety and efficacy populations.

8.3. Safety conclusions

A total of 21.6% of patients reported at least one ADR, whereas serious ADRs were reported by 3.2% of patients. The most frequent ADRs (>1%) in terms of % of affected patients were bone pain (5.86%), myalgia (3.43%), back pain (1.83%), arthralgia (1.68%) and pyrexia (1.14%). All the other ADRs had a frequency lower than 1%. As a consequence of ADRs or SADRs, the study was discontinued in 2.3% of patients.

Lipegfilgrastim is well tolerated in the real-world setting administered either in primary or secondary prophylaxis in patients with solid or haematological malignancies receiving cytotoxic CT.

Safety data obtained in this study are in line with published data for lipegfilgrastim and are expected for G-CSFs.

9. OVERALL CONCLUSIONS

In this non-interventional studies patients with solid or haematological malignancies treated with myelosupressive chemotherapy received Lonquex in primary or secondary prophylaxis, whereby majority of patients received it in primary prophylaxis (82.9%).

Among those receiving it a primary prophylaxis 82.4% of patients received Lonquex starting from chemotherapy cycle 1. In chemotherapy cycle 1, Lonquex was administered on time after the CT cycle (no delay; i.e. Lonquex was administered one day after the last administration of chemotherapeutic agent in the respective cycle) in 898 cycles (98.0%). The time delay went from 2 to 30 days in the 12 cycles (1.3%) where Lonquex was not administered on time after the CT cycle.

Lipegfilgrastim is effective and well tolerated in the real-world setting administered either in primary or secondary prophylaxis in patients with different tumor types receiving cytotoxic CT, both in terms of CT dose modifications and incidences of febrile neutropenia and grade 3/4 neutropenia.

Both effectiveness and safety data obtained in this study are in line with published data for lipegfilgrastim [1,9-13].

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