EPIDEMIOLOGY STUDY PROTOCOL

Drug Utilization Study of ZALTRAP® (aflibercept) Using European Databases

AVE005 Aflibercept

Study code: AFLIBC06660

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This study will be conducted in accordance with Sanofi standard operating procedures for epidemiologic studies

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STUDY SYNOPSIS

Drug name:	ZALTRAP® (aflibercept)
Title:	Drug utilization study (DUS) of ZALTRAP using European databases

Background:	ZALTRAP is a novel recombinant human fusion protein consisting of portions of the receptors for the vascular endothelial growth factor (VEGF) molecule. It is indicated for use in combination with irinotecan/ 5fluorouracil/ leucovorin (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin-containing regimen. In October of 2011, Sanofi filed a registration application with European Medicines Agency (EMA) for ZALTRAP to be marketed in the European Union (EU). Marketing authorization was granted for ZALTRAP on February 1st, 2013, following a positive opinion and recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) in November 2012. Other targeted agents approved for mCRC include bevacizumab (AVASTIN®), an anti-angiogenesis agent that binds all isoforms of VEGF-A, and cetuximab (ERBITUX®), and panitumumab (VECTIBIX®), both of which target the epidermal growth factor receptor (EGFR) pathway. The indications for some of these agents have been expanded beyond the initial mCRC indication. Bevacizumab indications also include metastatic breast cancer, metastatic or recurrent non-small-cell lung cancer, renal cell carcinoma, and ovarian cancer. Cetuximab also received a subsequent indication for head and neck cancer. The precedent of expanded indications for mCRC-approved targeted agents, both within forms of CRC and across tumor types, poses a risk that patients may be exposed to ZALTRAP for indications beyond what has been initially approved. The potential for ZALTRAP exposures for non-cancer treatments also exist. The off-label intravitreal use of VEGF inhibitors formulated for oncology use, such as AVASTIN, in the treatment of wet age-related macular degeneration (AMD) has been observed, despite the availability of a formulation for intravitreal use (LUCENTIS® [ranibizumab]). Because AVASTIN has similar target specificity as LUCENTIS, ophthalmologists have been treating wet AMD with AVASTIN prior to and following the approval of LUCENTIS. EYLEA® (aflibercept), a similar aflibercept drug substance was developed for intravitreal injection to treat wet AMD. There is potential for serious consequences if ZALTRAP is administered intravitreally, particularly since it is formulated as a hyperosmotic solution. Special warnings and precautions have been added in the ZALTRAP EU SmPC, package leaflet and packaging (for both vial and carton) to prevent the off-label intravitreal use of ZALTRAP. During the registration application with EMA for ZALTRAP to be marketed in the EU, Sanofi proposed a three-year DUS using European databases as part of the post-approval commitments. The primary objectives of the proposed DUS were to monitor ZALTRAP use in cancer patients including potential off-label use and evaluate the potential for intravitreal use.

Objectives:	The primary objectives are: • To evaluate the frequency distribution of cancer type(s) among patients who receive treatment containing ZALTRAP in the five largest national markets in Europe (EU5): United Kingdom (UK), France, Germany, Italy, and Spain. • To describe different treatment combinations among patients who receive therapy containing ZALTRAP in the EU5. • To evaluate the proportion of ZALTRAP patients with observed intravitreal use in England.
Study design:	Cross-sectional study

Data sources:	***Evaluation of ZALTRAP Use Among Cancer Patients*** Data for this study will be drawn from the IMS Oncology Analyzer™ (OA), which is a quarterly structured survey of treated prevalence for over 25 leading solid tumors and hematological malignancies. Detailed data on the characteristics and treatment of patients from various countries in Asia and Europe are collected. Data for this study will be limited to that from the EU5. The survey is completed by physicians recruited from hospitals and oncology centers. These physicians are recruited systematically to maximize the representativeness of their patient panels to care rendered in each country. Data including patients' demographics, cancer treatment details and specialty of treating physicians are collected only one time for each patient via paper-based medical record abstraction form. This system provides a way to track the usage of oncology products including ZALTRAP across all cancer types in the EU5. ***Evaluation of Intravitreal Use of ZALTRAP*** IMS Hospital Treatment Insights (HTI) is a linked database combining UK National Health Service (NHS) Hospital Episode Statistics (HES) data with the IMS Hospital Pharmacy Audit (HPA) data. HES is a data warehouse containing details of all admissions and visits to NHS hospital trusts, which provide inpatient, emergent, and outpatient specialty care in England. The HPA data provides a comprehensive record of usage of medicinal products by NHS hospitals, regardless of their source of supply. As of Q1 2012, the HPA audit covered 218,044 (93.63%) acute NHS beds. The linked data include 2.1 million patients from 33 of 166 hospital trusts in England; patients seeking care in UK geographies other than England are not represented in the HTI database. IMS integrates the combined HTI asset under procedures governed by the international security standard, ISO 270001. HTI provides HES and HPA data at the individual patient level, and contains patient demographics, diagnoses, procedures, and treatment characteristics. The database is updated quarterly and published once each calendar year with services ending in March of that year.

Study period:	ZALTRAP is expected to launch in Q1 2013 in Germany and the UK, and Q3 2013 in Spain, Italy, and France. The study period includes ZALTRAP exposures from first observed date of launch through 31 March 2016. In the OA database study of ZALTRAP use among cancer patients, this will include patients surveyed in the Q1 2013 through the Q1 2016 surveys. In the HTI database study of intravitreal use of ZALTRAP, this will include patient services through 31 March 2016. Analyses are planned for ZALTRAP exposures observed in three distinct time periods: first observed date of launch through 31 March 2014, 1 April 2014 through 31 March 2015, and 1 April 2015 through 31 March 2016.
Study population:	***Evaluation of ZALTRAP Use Among Cancer Patients*** *Inclusion criterion* • Patients with a record of the receipt of at least one dose of ZALTRAP during the study time periods, as determined by the drug brand name recorded in the current drug therapy field. *Exclusion criterion* • Patients who are participating in a clinical trial. ***Evaluation of Intravitreal Use of ZALTRAP*** *Inclusion criteria* • Patients with a record for the receipt of at least one dose of ZALTRAP during the study time periods; only the first exposure to ZALTRAP will be considered for each patient. o ZALTRAP use will be determined by the presence of the Anatomic Therapeutic Classification (ATC) code (ATC L01XX44) from the HPA drug ordering table in HTI and the brand name from the HPA drug reference tables in HTI. • For patients with prior exposure to EYLEA (ATC S01LA05), a subsequent exposure to ZALTRAP is required. *Exclusion criterion* • Patients exposed to EYLEA without subsequent exposure to ZALTRAP.

Exposure measurement:	ZALTRAP use is the main exposure of interest in both study database studies. Treatment with ZALTRAP will be captured using brand name recorded in the current drug therapy field in the OA database. In the HTI database, ATC code (ATC L01XX44) and brand name will be used to identify ZALTRAP use. Exposures to EYLEA (ATC S01LA05) will not be counted as exposures to ZALTRAP.
Outcomes of interest:	***Evaluation of ZALTRAP Use Among Cancer Patients*** The primary outcomes of interest in the database study of ZALTRAP use among cancer patients are: • The primary indication (tumor and stage) observed with ZALTRAP exposure, and • The concurrent therapies observed with ZALTRAP exposure. ***Evaluation of Intravitreal Use of ZALTRAP*** The primary outcome for this analysis is the intravitreal use of ZALTRAP.

Descriptive variables:	***Evaluation of ZALTRAP Use Among Cancer Patients*** • Demographic and clinical characteristics (reported for all patients): o Age group o Gender o Eastern Cooperative Oncology Group (ECOG) performance status at time of survey o Physician-reported comorbidities that affect treatment of cancer o Specialty of physician currently overseeing oncology treatment • Tumor characteristics (reported for a sub-set of patients with CRC recorded as the primary cancer site without evidence of metastasis): o Stage at diagnosis o Stage at first relapse o Tumor size, Lymph Nodes affected, Metastases (TNM) score at diagnosis o TNM score at first relapse • Treatment characteristics (reported for a sub-set of patients with CRC recorded as the primary cancer site): o Surgery before current therapy o Radiotherapy before current therapy o ZALTRAP dose per administration ***Evaluation of Intravitreal Use of ZALTRAP*** • Demographic and clinical characteristics (reported for all patients): o Age group o Gender o Ethnicity o Urbanicity o Diagnosis for which ZALTRAP was used o Specialty of prescriber or treating physician o Treatment setting

Stratifying variables:	The study outcomes and descriptive variables in the database study of ZALTRAP use among cancer patients will be reported overall and stratified separately by the country of origin (UK, France, German, Spain, and Italy). No stratifying variables will be employed in the database study that is estimating intravitreal ZALTRAP use.
Statistical analysis:	***Evaluation of ZALTRAP Use Among Cancer Patients*** Descriptive statistics of all demographics, tumor characteristics, treatment characteristics, and outcomes will be provided for all the countries combined and by each EU5 country, in each time period. Categorical variables will be presented as the count and percentage of patients in each category; continuous variables will be summarized by providing the mean, standard deviation, and median. One-sample 95% confidence intervals will be constructed around the point estimate for all outcomes. ***Evaluation of Intravitreal Use of ZALTRAP*** Descriptive statistics of all demographics, clinical characteristics, and outcomes will be reported for all patients in each time period. Categorical variables will be presented as the count and percentage of patients in each category. One-sample 95% confidence intervals will be constructed around each point estimate for all outcomes. ***Sample size*** This study will include all patients who receive therapy containing ZALTRAP in the OA database and all patients who receive ZALTRAP from the HTI database during the three-year study period. The estimated precision of 95% confidence intervals (CIs) around potential rates of off-label ZALTRAP use in the first year of the study were calculated using the observed first-year prevalence of cetuximab (N=25) or panitumumab (N=150). If the first-year N=25, the estimated 95% CIs for 1%, 5%, and 10% off-label ZALTRAP use would be 0.0% to 4.9%, 0.0% to 13.5%, and 0.0% to 21.8%, respectively. If the first-year N=150, the estimated 95% CIs for 1%, 5%, and 10% off-label ZALTRAP use would be 0.0% to 2.6%, 1.5% to 8.5%, and 5.2% to 14.8%, respectively.

Limitations:

Evaluation of ZALTRAP Use Among Cancer Patients

The OA database includes data from panels of physicians, who review current treatment and medical history from patients presenting for treatment. Physicians are recruited systematically to maximize the representativeness of their patient panel to care rendered in their respective countries, but participation of physicians is voluntary. The degree of bias between the sampling frame and recruited physicians, and the implications that such bias may have on the representativeness of ZALTRAP utilization within each country, is unknown.

The study will only report the first ZALTRAP use per patient, based on treatment history at the time of patient sampling. In the OA database, patients are not re-assessed to capture future treatments and outcomes. As a result, the study may miss ZALTRAP use for existing patients if it occurs after the date of assessment.

Finally, the study will use data from five out of 28 EU countries where marketing authorization was granted. Findings from the EU 5 countries may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions.

Evaluation of Intravitreal Use of ZALTRAP

The study is designed to capture only the first ZALTRAP exposure for each patient; therefore, subsequent exposures to ZALTRAP for the same patient will not be reported. Results should be interpreted as reflecting patients with initial use of ZALTRAP, rather than total ZALTRAP administrations.

In the HTI database, complete patient-level history is captured on drugs dispensed to patients through the hospital pharmacy. Drugs given to patients from the ward stock cannot be linked to an individual patient. Because ZALTRAP is a specialty pharmaceutical product, it is not expected to be included as a ward stock. However, it is likely that ZALTRAP for intravitreal administration will be prepared for in an aseptic unit. When drugs are sent via an aseptic unit, it is possible that complete patient-level detail may not be captured. The occurrence of this could lead to underreporting of potential intravitreal use of ZALTRAP since patients' history may not available.

The HTI database only allows for the assessment of intravitreal use of ZALTRAP in England. Therefore, the findings from this analysis may not be generalizable to the rest of the UK or to other EU countries where ZALTRAP will be marketed. Additionally, HTI data are collected from select hospital trusts that provided consent for their data to be linked to HPA. As a result, findings may only be generalizable to other trusts with similar population and clinical practices.

Data protection procedures:	***Evaluation of ZALTRAP Use Among Cancer Patients*** OA is a database of patient-anonymous (de-identified) healthcare activity and medical history. IMS Health does not maintain patient-identifiable information, or pseudonymous identifiers that can be linked back to individual patients, anywhere in the data production environment. Source documentation used for data entry is stripped of any potentially identifying marks. IMS Health adheres to relevant data retention guidelines for records and documents in both electronic and hard copy formats. As a fully de-identified database, analyses of OA are exempt from personal information requirements of Directive 95/46/EC of the European Parliament and of the Council (EU Directive). Further, because information in OA is patient-anonymous, no ethics or human subjects reviews are required. ***Evaluation of Intravitreal Use of ZALTRAP*** HTI is a pseudonymous database of patient healthcare activity. No patient-identifiable information is held anywhere within the data production environment. Linkage of source data occurs external to the data production environment, under the auspices of Health & Social Care Information Centre (HSCIC), and governed by a National Ethics Approval (Research Ethics Committee – [REC]) and National Information Governance Board (NIGB) Section 251. Additional review of patient privacy and security protections have been provided by the UK Department of Health and by the Medicines and Healthcare Products Regulatory Agency (MHRA), who have provided letters of support. Under a directive from the UK National Health Service, individual studies conducted using HTI data require approval of the study protocol from Independent Scientific Ethics and Advisory Committee (ISEAC). However, as a pseudonymous database of historical healthcare activity, informed consent from study subjects is not required.

Timelines:	Three separate analyses are planned for this study. Data for the first analysis will include the first observed date of ZALTRAP launch through 31 March 2014. Data for the second analysis will include the time period from 1 April 2014 through 31 March 2015. Data for the final analysis will include the time period from 1 April 2015 through 31 March 2016. OA records are released for analysis 45 days after the end of each calendar quarter. HTI records from a complete HES data year will be available approximately 4 months after the close of the data year (31 March). Each report will be submitted on 30 November of the same year after the end of the relevant data period. The first report will be delivered 30 November 2014, the second report will be delivered 30 November 2015, and the last report will be delivered 30 November 2016.

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LIST OF ABBREVIATIONS

Abbreviation	Description
A&E	Accident and Emergency
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
DUS	Drug Utilization Study
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EU	European Union
EU5	United Kingdom, France, German, Italy, and Spain
FOLFIRI	Irinotecan/5-fluorouracil/leucovorin
HSCIC	Health & Social Care Information Centre
HES	Hospital Episode Statistics, a National Health Service database
HIV	Human immunodeficiency virus
HPA	IMS Hospital Pharmacy Audit database
HTI	IMS Hospital Treatment Insights database
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
INN	International Nonproprietary Name
ISEAC	Independent Scientific Ethics and Advisory Committee
mCRC	Metastatic Colorectal Cancer
MHRA	Medicines and Healthcare Products Regulatory Agency
NIGB	National Information Governance Board
NHS	National Health Service
OA	IMS Oncology Analyzer
OPCS-4.6	Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision)
REC	Research Ethics Committee
SMPC	Summary of Product Characteristics
TNM Score	Tumor size, Lymph Nodes affected, Metastases Score
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor
Wet AMD	Wet Age Macular Degeneration

1 INTRODUCTION

ZALTRAP® (aflibercept) is a novel recombinant human fusion protein consisting of portions of the receptors for the vascular endothelial growth factor (VEGF) molecule.[1] It binds to VEGF-A, VEGF-B, and placental growth factors.[1] ZALTRAP is indicated for use in combination with irinotecan/5-fluorouracil/leucovorin (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.

In October 2011, Sanofi filed a registration application with the European Medicines Agency's (EMA) for ZALTRAP to be marketed in the European Union (EU). ZALTRAP has been granted marketing authorization in the EU on February 1st 2013, following a positive opinion and recommendation from EMA's Committee for Medicinal Products for Human Use (CHMP) in November 2012.[2] The recommendation and approval was based on data from the pivotal Phase III VELOUR study, a multinational, randomized, double-blind trial comparing FOLIFIRI in combination with either ZALTRAP or placebo in the treatment of patients with mCRC previously treated with an oxaliplatin-containing regimen.[3]

Other targeted agents approved for mCRC include bevacizumab (AVASTIN®), an anti-angiogenesis agent that binds all isoforms of VEGF-A, and cetuximab (ERBITUX®), and panitumumab (VECTIBIX®), both of which target the epidermal growth factor receptor (EGFR) pathway.[4,5,6] Like ZALTRAP, bevacizumab inhibits angiogenesis through binding to VEGF, while cetuximab and panitumumab inhibit tumor growth through binding to the EGFR. Targeted agents have been available for treatment of mCRC in Europe since 2004, and some agents have added indications for first-line therapy after initial approval for second- or third-line therapy. In addition, bevacizumab indications in Europe have expanded beyond the initial mCRC indication to include metastatic breast cancer, metastatic or recurrent non-small-cell lung cancer, renal cell carcinoma, and ovarian cancer. Cetuximab also received a subsequent indication for head and neck cancer. The precedent of expanded indications for mCRC-approved targeted agents, both within forms of CRC and across tumor types, poses a risk that patients may be exposed to ZALTRAP for indications beyond what has been initially approved.

The potential for ZALTRAP exposures for non-cancer treatments also exist. The off-label intravitreal use of VEGF inhibitors formulated for oncology use in the treatment of neovascular or wet age-related macular degeneration (AMD) has been widely documented, despite the availability of VEGF formulations specifically for the treatment of wet AMD.[4,7,8,9] LUCENTIS® (ranibizumab), an affinity-matured antigen-binding fragment (Fab) derived from bevacizumab, was developed specifically for intravitreal administration to treat wet AMD, and is formulated as an iso-osmotic solution.[1,9] LUCENTIS was developed as a Fab because the smaller size was thought to enhance its diffusion from the vitreous into the retina and choroid, relative to full-length antibodies.[1] Because AVASTIN has similar target specificity to LUCENTIS, ophthalmologists have been observed treating wet AMD with AVASTIN prior to and after the approval of LUCENTIS.[7,10]

ZALTRAP was formulated for systemic (intravenous) administration, and specifically for the needs of oncology patients. ZALTRAP was formulated as a hyperosmotic solution to facilitate the long-term stability of the formulation prior to its dilution and administration.[1] Similar to AVASTIN and LUCENTIS, a similar aflibercept drug product, known as EYLEA® (aflibercept), an ultra-purified and iso-osmotic drug, was developed specifically for intravitreal injection for use in the treatment of wet AMD. Because of the precedent of off-label use of AVASTIN for wet AMD, patients may be at risk for off-label intravitreal administration of ZALTRAP. ZALTRAP may have potential for serious consequences when administered intravitreally. While the effect of intravitreal use of ZALTRAP has not been studied, retinal detachment and permanent retinal degeneration have been reported in animal studies where hyperosmotic solutions were administered intravitreally.[11] Special warnings and precautions have been added in the ZALTRAP EU SmPC, package leaflet and packaging (for both vial and carton) to prevent the off-label intravitreal use of ZALTRAP.

To determine the extent of off-label use of ZALTRAP after its availability in the EU, Sanofi proposed a three-year Drug Utilization Study (DUS) using European databases as part of the post-approval commitments, during the registration application with EMA for ZALTRAP to be marketed in EU. The primary objectives of the proposed DUS were to monitor ZALTRAP use in cancer patients including potential off-label use and evaluate the potential intravitreal use.

2 STUDY OBJECTIVES

The study aims to evaluate the extent of off-label use of ZALTRAP following its availability in the market. This evaluation has two components: 1) use in cancer patients including off-label use in cancer type(s) and in combinations other than those described in the label; 2) intravitreal use.

The specific primary objectives of the study are:

- To evaluate the frequency distribution of cancer type(s) among patients who receive treatment containing ZALTRAP in the five largest national markets in Europe (EU5): United Kingdom (UK), France, Germany, Italy, and Spain.

- To describe different treatment combination among patients who receive therapy containing ZALTRAP in the EU5.

- To evaluate the proportion of ZALTRAP patients with observed intravitreal use in England.

3 METHODS

3.1 STUDY DESIGN

This will be a cross-sectional study of two main samples of patients with exposure to ZALTRAP, identified at three different time points (first interim, second interim, and final analysis). The first sample will include cancer patients treated with ZALTRAP in the EU5; frequencies of tumor types recorded for treatment with ZALTRAP and treatment combinations containing ZALTRAP will be reported from this sample. The second sample will include English patients visiting hospital trusts and receiving exposure to ZALTRAP for any indication; the proportion of intravitreal ZALTRAP administrations will be reported from this sample.

3.1.1 Source populations/databases used

Two databases will be used to construct the respective study patients. Data for the evaluation of ZALTRAP use among cancer patients will be drawn from the IMS Oncology Analyzer™ (OA). Data for the evaluation of intravitreal use of ZALTRAP will be drawn from the IMS Hospital Treatment Insights (HTI) database. Descriptions of each database appear below.

IMS Oncology Analyzer

The IMS Oncology Analyzer is a quarterly structured survey of treated prevalence for over 25 leading solid tumors and hematological malignancies. It contains detailed data on the characteristics and treatment of patients with a variety of tumor types in Asia (Japan, China, Korea, Taiwan) and Europe (EU5, the Netherlands, and Turkey). Only data for the EU5 will be used for this study.

The physician sampling frame for each EU country was created from an IMS census of practitioners treating cancer patients within each country. The physicians contracted to complete OA surveys are recruited systematically to maximize the representativeness of their patient panels to care rendered in each country.

Contracted physicians sample a pre-specified number of consecutive patients in a designated week during the calendar quarter, with the size of the sample determined by their total patient panel and the share of patients with various tumor types that they treat within their country. Data are collected one time for each patient from physicians in oncology settings using a structured, paper-based medical record abstraction form. The data collection includes all patient history available in the reporting physician's records, meaning that historical longitudinal information is available. However, patients are not resampled, so records are not updated with future treatment or outcomes information after the patient's initial survey date.

Data elements include patient demographics, tumor stage and diagnostic test results at various points during past treatment, past surgery and radiotherapy, and past and current chemotherapy, hormonal therapy, and supportive care. The database currently includes data on nearly 60,000 unique patients treated by nearly 2,300 physicians, including nearly 14,000 patients and more than 860 physicians in the EU5. Data are available from the first quarter (Q1) of 2005, with a data lag of 45 days following the end of each quarter.

IMS Hospital Treatment Insights

IMS Hospital Treatment Insights (HTI) is a linkage of private and public secondary care assets in England. Pharmacy records come from a proprietary audit of hospital trusts in the UK National Health Service (NHS) maintained by IMS Health. The IMS Hospital Pharmacy Audit (HPA) provides a comprehensive record of usage of medicinal products by NHS hospitals dating back to 1991. It monitors usage/consumption levels by end user hospitals, rather than wholesale purchases by the facilities themselves. HPA monitors usage of all pharmaceutical products within the hospital, regardless of their source of supply. Product sales from wholesalers, direct from manufacturers, or via other hospitals are all automatically covered. As of Q1 2012, the audit had a universe size of 232,888 total NHS beds and 218,044 acute NHS beds. In terms of data coverage, 93.63% of hospital acute beds are effectively covered. The audit does not currently cover the private or military sectors.

HPA records are linked to Hospital Episode Statistics (HES) records published by NHS. HES is a data warehouse containing details of all admissions and visits to NHS hospital trusts, which provide inpatient, emergent, and outpatient specialty care in England. HES contains admitted patient care data from 1989 onwards, with more than 12 million new records added each year, and outpatient attendance data from 2003 onwards, with more than 40 million new records added each year.

IMS integrates the combined HTI asset under procedures governed by the international security standard, ISO 270001. HTI contains diagnoses (ICD10 format), procedures (OPCS-4.6 format), and several A&E (Accident and Emergency) clinical classification codes. The ‘OPCS Classification of Interventions and Procedures’ (OPCS-4.6) is a procedural classification list for the coding of operations, procedures and interventions performed on NHS patients during an Episode of health care in the UK. The HES portion of HTI comprises inpatient admissions, outpatient specialist appointments and treatments, and Accident & Emergency admissions.

The linked data include 2.1 million patients across all different hospital therapies. HES data are currently contributed from 33 of 166 hospital trusts in England; as a result, some patients may be represented by hospital trust pharmacy records (HPA) without corresponding links to specialist, inpatient, or A&E visits. Patients seeking care in UK geographies other than England are not represented in the HTI database.

A HES data year runs from April 1st (Q2) until the following March 31st (Q1). Provisional HES data come in quarterly and are "restated" (updated) each quarter until a year is complete. There is an NHS requirement that patient-level HES data must reside within the UK geography, within an ISO27001 accredited data centre; therefore, analyses of HTI are managed by accredited IMS analysts in the UK.

3.1.2 Study period

ZALTRAP is expected to launch in Q1 2013 in Germany and the UK, and Q3 2013 in Spain, Italy, and France. The study period includes ZALTRAP exposures from first observed date of launch through 31 March 2016.

In the OA database study of ZALTRAP use among cancer patients, this will include patients surveyed in the Q1 2013 through the Q1 2016 surveys.

In the HTI database study of intravitreal use of ZALTRAP, this will include patient services through 31 March 2016, which coincides with the end of the 2015-2016 HES data year.

Analyses are planned for ZALTRAP exposures observed in three distinct time periods: first observed date of ZALTRAP launch through 31 March 2014, 1 April 2014 through 31 March 2015, and 1 April 2015 through 31 March 2016. See Section 7 (STUDY TIMELINES).

3.1.3 Study population

To address the study objectives, two main samples of patients with exposure to ZALTRAP will be identified. Patients who meet the study selection criteria described below will be selected into the study.

Patient Selection Criteria – Evaluation of ZALTRAP Use Among Cancer Patients

Inclusion criterion

Patients meeting the following inclusion criteria will be initially selected for study inclusion:

- Patients from the EU5 for whom the physician reported the receipt of at least one dose of ZALTRAP, as a current therapy, in the time periods described above. ZALTRAP use will be identified by the brand name recorded in the current drug therapy field.

Exclusion criterion

- Participation in a clinical trial will exclude patients from the study.

Patient Selection Criteria – Evaluation of Intravitreal Use of ZALTRAP

Inclusion criteria

Patients meeting the following inclusion criteria will be initially selected for study inclusion:

- Patients with a record for the receipt of at least one dose of ZALTRAP during the study time periods described above. Only the first exposure to ZALTRAP will be identified for each patient throughout the study period, so that patients are included only once in the study population.
    - The receipt of ZALTRAP will be identified using the Anatomic Therapeutic Classification (ATC) code from the HPA drug ordering table in HTI and the brand name from the HPA drug reference tables in HTI. Exposure to ZALTRAP will use the ATC L01XX44 code.
- For patients with prior exposure to EYLEA (ATC S01LA05), a subsequent exposure to ZALTRAP is required.

Exclusion criterion

- Patients exposed to EYLEA without subsequent exposure to ZALTRAP will be excluded from the study population.

This is a cross-sectional study of patients with initial drug exposure to ZALTRAP. Longitudinal patient episodes will not be constructed for the analysis. Therefore, no minimum enrollment or registration period will be required for patients before or after ZALTRAP exposure.

3.2 EXPOSURE MEASUREMENT

The main exposure of interest in both database studies is treatment with at least one dose of ZALTRAP. ZALTRAP exposure in the OA database will be identified by the brand name recorded in the current drug therapy field. IMS data entry staff code and standardize the free text responses reported by physicians on survey forms to assure that drug exposures are consistently recorded in the database and correspond to standard naming conventions.

In the HTI database, ATC code and brand name will be used to identify ZALTRAP use. Exposure to ZALTRAP will use the ATC L01XX44 code. Exposures to EYLEA (ATC S01LA05) will not be counted as exposures to ZALTRAP.

3.3 OUTCOMES OF INTEREST

Outcome Assessment – Evaluation of ZALTRAP Use Among Cancer Patients

The primary outcomes of interest in the database study of ZALTRAP use among cancer patients are:

- The primary indication (tumor and stage) observed with ZALTRAP exposure, and
- The concurrent therapies observed with ZALTRAP exposure.

Diagnostic Indication

The diagnostic indication for treatment with ZALTRAP will be categorized as either label-approved indication or off-label indication. Label-approved indication will be defined as colorectal cancer recorded as the primary cancer site, with further evidence of metastasis. Metastasis may be characterized by a record of stage IV on or before current therapy, or a documented distant metastasis site even if a stage is reported other than stage IV. OA records tumor staging only at initial diagnosis and at first relapse; either stage will be considered for defining metastasis if the date associated with the reported stage is on or before the current therapy start date.

Off-label indications will be defined as other primary cancer diagnoses, or CRC that was not confirmed as metastatic. Primary cancer diagnoses captured under the off-label indication will be reported separately as follows:

- Non-mCRC (CRC diagnosis that was not confirmed as metastatic)
- Non-small-cell lung cancer (NSCLC), all stages
- Renal cell cancer, all stages
- Breast cancer, all stages
- Ovarian cancer, all stages
- Other cancers

Categorizes under off-label indications are expected to be mutually exclusive. However, these will be reported as non-mutually exclusive groups if more than one primary cancer site is recorded for some patients.

Concurrent treatments with ZALTRAP

Concurrent treatments with ZALTRAP will be defined as current cytotoxic therapies reported along with ZALTRAP therapy. Current hormonal or supportive drug therapies used concurrently with ZALTRAP will not be reported. Treatment combinations containing ZALTRAP will be categorized as follows:

- ZALTRAP with irinotecan/5-fluorouracil/leucovorin (FOLFIRI)[1]
- Non-label-recommended combinations
    - ZALTRAP monotherapy

[1] Due to reimbursement restriction for some chemotherapy agents in some EU5 countries, ZALTRAP use may be observed with FOLFIRI-like protocols that exclude irinotecan. We may consider a separate category that reports 5-FU/leucovorin excluding irinotecan should sufficient cases with this pattern be observed.

- ZALTRAP with other cytotoxic agents
- ZALTRAP with other mCRC approved targeted agents (See Appendix B)

Outcome Assessment – Evaluation of Intravitreal Use of ZALTRAP

The primary outcome for this analysis is intravitreal use of ZALTRAP. Any administration of ZALTRAP that meets the criteria described below will be defined as intravitreal use of ZALTRAP:

- The presence of an intravitreal route of administration recorded for the administration of ZALTRAP.
- Prescription of ZALTRAP by an ophthalmologist with no observable patient diagnosis code for CRC (ICD-10 codes: C18.x, C20.x, C21.x; See Appendix A for description of codes).
- ZALTRAP administered with a diagnosis code of wet AMD (ICD-10 code: H35.3x; See Appendix A for description of codes) with no observable patient diagnosis code for CRC.

3.4 DESCRIPTIVE VARIABLES

Descriptive Variables – Evaluation of ZALTRAP Use Among Cancer Patients

Demographic Characteristics

Patient demographic characteristics will be presented based on data collected at the time of the survey, and will be reported for all patients. These data will include:

- Age (reported in categories):
  - 0 – 15
  - 16 – 25
  - 26 – 35
  - 36 – 45
  - 46 – 55
  - 56 – 65
  - 66 – 75
  - 76 +
- Gender:
  - Male

- Female

Clinical Characteristics

Clinical characteristics will be presented based on data collected at the time of the survey, and will be reported for all patients. These data will include:

- Eastern Cooperative Oncology Group (ECOG) performance status at time of survey:
  - 0, asymptomatic
  - 1, symptomatic, fully ambulatory
  - 2, symptomatic, in bed <50% of day
  - 3, symptomatic, in bed >50% of day, but not bedridden
  - 4, bedridden

- Physician-reported comorbidities that affect treatment of cancer (The survey has a pre-determined list of comorbidities for physicians to select. The categories below are not mutually exclusive):
  - Cardiac dysfunction
  - Chronic obstructive pulmonary disease (COPD)
  - Diabetes
  - Human immunodeficiency virus (HIV)
  - Liver dysfunction
  - Parkinson's
  - Renal dysfunction
  - Other
  - None

- Specialty of physician currently overseeing oncology treatment:
  - Medical oncologist
  - Clinical oncologist
  - Gastroenterologist
  - Gynecologist
  - Urologist
  - Hematologist
  - Surgeon
  - Other

Tumor Characteristics

Tumor characteristics will be reported for the sub-set of patients with CRC recorded as the primary cancer site, without evidence of metastasis. Specific variables will include:

- Stage at diagnosis:
    - 0
    - I
    - II
    - III
    - IV
- Stage at first relapse:
    - 0
    - I
    - II
    - III
    - IV
    - No relapse recorded
- Tumor size, Lymph Nodes affected, Metastases (TNM) score at diagnosis:
    - T
        - T1
        - T2
        - T3
        - T4
    - N
        - N0
        - N1
        - N2
        - N3
    - M
        - M0
        - M1
- TNM score at first relapse:
    - T
        - T1
        - T2

        - T3
        - T4
    - N
        - N0
        - N1
        - N2
        - N3
    - M
        - M0
        - M1

Treatment Characteristics

Treatment information will be presented based on data collected at the time of the survey, and will be reported for patients with CRC recorded as the primary cancer site. These data will include:

- Surgery:
    - Any curative surgery before current therapy (yes/no)
    - Any palliative surgery before current therapy (yes/no)
- Any radiotherapy before current therapy (yes/no)
- ZALTRAP dose per administration (The recommended dose of ZALTRAP is 4mg/kg. Dose of ZALTRAP per administration will be calculated based on information available in the quantity per dose, dose unit, and weight fields of the survey; and will be reported in mg/kg. When mg is selected as the unit for quantity per dose, the dose administered will be calculated by dividing the quantity per dose by weight. If mg/kg is selected as the unit for quantity per dose, the dose administered will be used as recorded. ZALTRAP dose will not be calculated for patients with missing records for any of the required fields.)

Descriptive Variables – Evaluation of Intravitreal Use of ZALTRAP

Demographic and clinical characteristics will be presented based on data collected at the time of the first ZALTRAP administration. These data will include:

- Age (reported in whole years, during year of first administration)
    - 0 – 15
    - 16 – 25
    - 26 – 35

- 36 – 45
- 46 – 55
- 56 – 65
- 66 – 75
- 76 +

- Gender:
  - Male
  - Female
- Ethnicity
  - White (British, Irish, any other White background)
  - Black / British Black (Caribbean, African, any other Black background)
  - Asian /Asian British (Indian, Pakistani, Bangladeshi, any other Asian background)
  - Other (White and Black Caribbean, White and Black African, White and Asian, any other Mixed background, Chinese, any other ethnic group)
  - Not stated / unknown
- Urbanicity:
  - Urban
  - Rural
- Diagnosis for which ZALTRAP was used:
  - Colorectal cancer
  - Other cancers (ICD-10 codes: C00.x – C17.0, C19.x, C22.x – D48.x; See Appendix A for description of codes)
  - Wet AMD (ICD-10 codes: H35.3; See Appendix A for description of codes)
  - Diabetic macular edema (ICD-10 codes: H35.8x, E10.3x, E11.3x; See Appendix A for description of codes)
  - Other diagnoses
- Specialty of prescriber or treating physician:
  - Ophthalmologist
  - Oncologist
  - Other physician specialties
- Treatment setting:

- Inpatient
- Outpatient

3.5 STRATIFYING VARIABLES

The study outcomes and descriptive variables in the database study of ZALTRAP use among cancer patients will be reported overall and stratified separately by the following variables:

- Country of origin:
  - UK
  - France
  - Germany
  - Spain
  - Italy

No stratifying variables will be employed in the database study that is estimating intravitreal ZALTRAP use.

3.6 SAMPLE SIZE AND POWER CALCULATION

This study will include all patients who receive therapy containing ZALTRAP in the OA database and all patients who receive ZALTRAP from the HTI database during the three-year study period.

Historical prevalence of ZALTRAP treatment is not available. In the OA database, we have observed the first-year prevalence of current therapies for angiogenesis inhibitors cetuximab (EC authorized 29 June 2004) and panitumumab (EC authorized 12 March 2007), both of which were initially approved for second-line or later indications. OA captured 153 patients with current cetuximab therapy in the four quarters ending Q2 2005, and 23 patients with current panitumumab therapy in the first four quarters ending Q1 2008. Due to the limitations on data history in the HTI database, no equivalent treatment prevalence estimates are available.

In the table below, we have reported the precision of 95% confidence intervals around various potential rates of off-label ZALTRAP use in the first year of the study period. We have rounded the potential sample sizes, based on observed first-year prevalence of cetuximab or panitumumab, to multiples of 25.

Exhibit 1. 95% Confidence Interval Estimates for Potential Rates of Off-Label ZALTRAP Use

Potential first-year sample	1% off label use	5% off label use	10% off label use
N=25	95% CI (0.0%, 4.9%)	95% CI (0.0%, 13.5%)	95% CI (0.0%, 21.8%)
N=150	95% CI (0.0%, 2.6%)	95% CI (1.5%, 8.5%)	95% CI (5.2%, 14.8%)

4 STATISTICAL ANALYSIS

Statistical Analysis – Evaluation of ZALTRAP Use Among Cancer Patients

- Univariate descriptive statistics will be conducted to characterize the all patients. All analyses will be reported for all the countries combined and separately for each EU5 country. Tables 1 to 5 in section 10 (Tables) represent sample tables to be generated for the analyses. All tables will be replicated for each time period.

- The demographic variables including age and gender will be reported for all cancer patients treated with ZALTRAP. Tumor characteristics will be described for a sub-set of cancer patients treated with ZALTRAP and with non-mCRC diagnosis. Treatment characteristics will be described for a sub-set of cancer patients treated with ZALTRAP and with CRC diagnosis. For categorical measures, the distribution of patients across the categories of each characteristic will be described using cross tabulation analysis, showing the frequency (number of cases) and percentage of the total number of study patients observed overall and by each EU5 country. For continuous measures, mean, median, and standard deviation will be computed overall and by each EU5 country.

All outcomes will be reported descriptively. The frequency (number of cases) and percentage of study patients for whom ZALTRAP was used according to the label-approved indication and label-recommended treatment combination will be reported overall and by each EU5 country.

For ZALTRAP use in an off-label indication and ZALTRAP used with non-label-recommended treatment combinations, the distribution of patients across the categories of each cancer type will be described using cross tabulation analysis, showing the frequency (number of cases) and percentage of the total number of study patients observed overall and by each EU5 country. One-sample 95% confidence intervals will be constructed around the proportion of off-label ZALTRAP use, and the proportion of ZALTRAP used with non-label-recommended treatment combinations, for each stratum.

Statistical Analysis – Evaluation of Intravitreal Use of ZALTRAP

- Univariate descriptive statistics will be conducted to characterize all patients. Tables 6 to 8 in section 10 (Tables) represent sample tables to be generated for the analyses. All tables will be replicated for each time period.

- All descriptive variables including demographics, diagnostic indication, and treatment characteristics will be reported. Frequency (number of cases) and percentage of the total number of study patients observed will be described for each variable.

All outcomes will be reported descriptively. The frequency (number of cases) and percentage of study patients with intravitreal use of ZALTRAP will be reported. One-sample 95% confidence intervals will be constructed around the proportion of intravitreal use of ZALTRAP.

5 LIMITATIONS

Oncology Analyzer–Evaluation of ZALTRAP Use Among Cancer Patients

The OA database includes data from panels of physicians, who review current treatment and medical history from patients presenting for treatment. Physicians are recruited systematically to maximize the representativeness of their patient panel to care rendered in their respective countries, but participation of physicians is voluntary. The degree of bias between the sampling frame and recruited physicians, and the implications that such bias may have on the representativeness of ZALTRAP utilization within each country, is unknown.

The study will only report the first ZALTRAP use per patient, based on treatment history at the time of patient sampling. In the OA database, patients are not re-assessed to capture future treatments and outcomes. As a result, the study may miss ZALTRAP use for existing patients if it occurs after the date of assessment.

Finally, the study will use data from five out of 28 EU countries where marketing authorization was granted. Findings from the EU 5 countries may not be generalizable to other EU countries where ZALTRAP received marketing authorization, as there might be different treatment guidelines, physician prescribing behaviors, reimbursement policies, or other utilization restrictions.

Hospital Treatment Insights – Evaluation of Intravitreal Use of ZALTRAP

The study is designed to capture only the first ZALTRAP exposure for each patient; therefore, subsequent exposures to ZALTRAP for the same patient will not be reported. Results should be interpreted as reflecting patients with initial use of ZALTRAP, rather than total ZALTRAP administrations.

The data captured in the HTI database is a combination of data collected from the IMS HPA and UK NHS HES databases. In the HTI database, complete patient-level history is captured on drugs dispensed to patients through the hospital pharmacy. Drugs given to patients from the ward stock cannot be linked to an individual patient. Because ZALTRAP is a specialty pharmaceutical product, it is not expected to be included as a ward stock, especially in specialty hospital outpatient setting. However, it is likely that ZALTRAP for intravitreal administration will be prepared in an aseptic unit. When drugs are sent via an aseptic unit, it is possible that complete patient-level detail may not be captured. The occurrence of this could lead to underreporting of potential intravitreal use of ZALTRAP since patients' history such as diagnosis, physician specialty information, or route of administration may not be available.

The HTI database only allows for the assessment of intravitreal use of ZALTRAP in England. Therefore, the findings from this analysis may not be generalizable to the rest of the UK or to other EU countries where ZALTRAP will be marketed. Additionally, HTI data are collected from select hospital trusts that provided consent for their data to be linked to HPA. As a result, findings may only be generalizable to other trusts with similar population and clinical practices.

6 DATA PROTECTION PROCEUDRES

Oncology Analyzer–Evaluation of ZALTRAP Use Among Cancer Patients

OA is a database of patient-anonymous (de-identified) healthcare activity and medical history. IMS Health does not maintain patient-identifiable information, or pseudonymous identifiers that can be linked back to individual patients, anywhere in the data production environment. Source documentation used for data entry is stripped of any potentially identifying marks. IMS Health adheres to relevant data retention guidelines for records and documents in both electronic and hard copy formats. As a fully de-identified database, analyses of OA are exempt from personal information requirements of Directive 95/46/EC of the European Parliament and of the Council (EU Directive). Further, because information in OA is patient-anonymous, no ethics or human subjects reviews are required.

Hospital Treatment Insights – Evaluation of Intravitreal Use of ZALTRAP

HTI is a pseudonymous database of patient healthcare activity. No patient-identifiable information is held anywhere within the data production environment. Linkage of source data occurs external to the data production environment, under the auspices of Health & Social Care Information Centre (HSCIC), and governed by a National Ethics Approval (Research Ethics Committee – [REC]) and National Information Governance Board (NIGB) Section 251. Additional review of patient privacy and security protections have been provided by the UK Department of Health and by the Medicines and Healthcare Products Regulatory Agency (MHRA), who have provided letters of support. Under a directive from the UK National Health Service, individual studies conducted using HTI data require approval of the study protocol from Independent Scientific Ethics and Advisory Committee (ISEAC). However, as a pseudonymous database of historical healthcare activity, informed consent from study subjects is not required.

7 STUDY TIMELINES

Three separate analyses are planned for this study. Data for the first analysis will include the time period through 31 March 2014. Data for the second analysis will include the time period from 1 April 2014 through 31 March 2015. Data for the final analysis will include the time period from 1 April 2015 through 31 March 2016.

OA records are released for analysis 45 days after the end of each calendar quarter. HTI records from a complete HES data year will be available approximately 4 months after the close of the data year (31 March). Each report will be submitted on 30 November of the same year after the end of the relevant data period. Therefore, the first report will be delivered 30 November 2014, the second report will be delivered 30 November 2015, and the last study report will be delivered 30 November 2016.

8 REFERENCES

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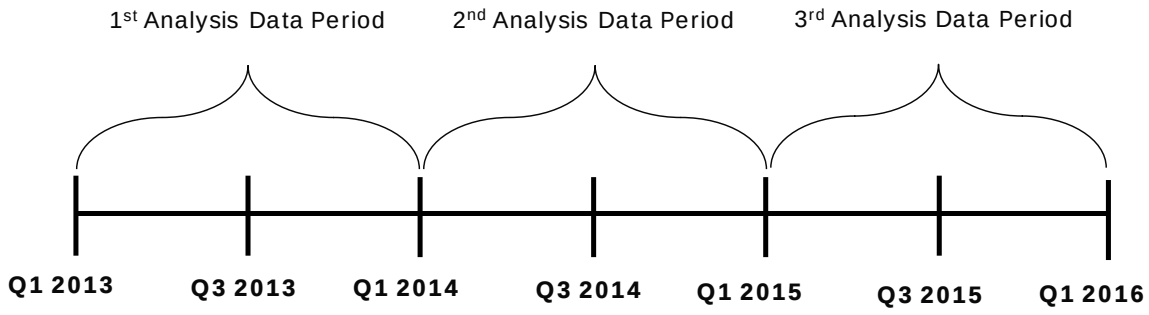
9 FIGURES

Figure 1. Graphic Illustration of the Study Period For OA and HIT Databases



10 TABLES

Table 1. Demographic Characteristics Among All Patients (OA Database).

Demographic Characteristics	**All Patients** (N =)	**UK** (N =)	**Germany** (N =)	**France** (N =)	**Spain** (N =)	**Italy** (N =)
Age Group (n, %)						
0 – 15						
16 – 25						
26 – 35						
36 – 45						
46 – 55						
56 – 65						
66 – 75						
76 +						
Sex (n, %)						
Male						
Female						

Table 2. Clinical Characteristics Among All Patients (OA Database).

Clinical Characteristics	**All Patients** (N =)	**UK** (N =)	**Germany** (N =)	**France** (N =)	**Spain** (N =)	**Italy** (N =)
ECOG performance status at time of survey (n, %)						
0						
1						
2						
3						
4						
Comorbidities (n, %)						
Cardiac dysfunction						
COPD						
Diabetes						
HIV						
Liver dysfunction						
Parkinson's						
Renal dysfunction						
Other						
None						
Physician specialty (n, %)						
Medical oncologist						
Clinical oncologist						
Gastroenterologist						
Gynecologist						
Urologist						
Hematologist						
Surgeon						
Other						

Table 3 Outcome Measures Among All Patients (OA Database).

Measures	**All Patients** (N =)			**UK** (N =)			**Germany** (N =)			**France** (N =)			**Spain** (N =)			**Italy** (N =)		
	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
Diagnostic indication for Zaltrap																		
Label-approved indication		-	-		-	-		-	-		-	-		-	-		-	-
Off-label indication																		
Non-mCRC		-	-		-	-		-	-		-	-		-	-		-	-
NSCLC, all stages		-	-		-	-		-	-		-	-		-	-		-	-
Renal cell cancer, all stages		-	-		-	-		-	-		-	-		-	-		-	-
Breast cancer, all stages		-	-		-	-		-	-		-	-		-	-		-	-
Ovarian cancer, all stages		-	-		-	-		-	-		-	-		-	-		-	-
Other cancers, all stages		-	-		-	-		-	-		-	-		-	-		-	-
Treatment combinations																		
Zaltrap with FOLFIRI		-	-		-	-		-	-		-	-		-	-		-	-
Non-label-recommended combinations																		
Zaltrap monotherapy		-	-		-	-		-	-		-	-		-	-		-	-
Zaltrap with other cytotoxic agents		-	-		-	-		-	-		-	-		-	-		-	-
Zaltrap with other mCRC targeted agents		-	-		-	-		-	-		-	-		-	-		-	-

Table 4. Tumor Characteristics Among Patients Diagnosed with Non-mCRC (OA Database).

Tumor Characteristics	**All Patients** (N=)	**UK** (N=)	**Germany** (N=)	**France** (N=)	**Spain** (N=)	**Italy** (N=)
Stage at diagnosis (n, %)						
0						
I						
II						
III						
IV						
Stage at first relapse (n, %)						
0						
I						
II						
III						
IV						
No relapse recorded						
TNM score at diagnosis (n, %)						
T						
T1						
T2						
T3						
T4						
N						
N0						
N1						
N2						
N3						
M						
M0						
M1						

TNM score at first relapse (n, %)						
T						
T1						
T2						
T3						
T4						
N						
N0						
N1						
N2						
N3						
M						
M0						
M1						

Table 5. Treatment Characteristics Among Patients Diagnosed with CRC (OA Database).

Treatment Characteristics	**All Patients** (N =)	**UK** (N =)	**Germany** (N =)	**France** (N =)	**Spain** (N =)	**Italy** (N =)
Surgery before current therapy (n, %) Any curative surgery Any palliative surgery						
Radiotherapy before current therapy (n, %)						
ZALTRAP dose per administration Mean SD Median						

Table 6. Demographic Characteristics Among All Patients (HTI Database).

Demographic Characteristics	**All Patients (England)** (N =)
Age (n, %)	
0 – 15	
16 – 25	
26 – 35	
36 – 45	
46 – 55	
56 – 65	
66 – 75	
76 +	
Sex (n, %)	
Male	
Female	
Ethnicity (n, %)	
White	
Black / British Black	
Asian / British Asian	
Other	
Not stated / unknown	
Urbanicity (n, %)	
Urban	
Rural	

Table 7. Proportion of Patients With Intravitreal Zaltrap Use (HTI Database)

Measures	**All Patients (England)** (N=)		
	N	%	95% CI
Intravitreal use of ZALTRAP			

Table 8. Clinical Characteristics Among All Patients (HTI Database).

Clinical Characteristics	**All Patients (England)** (N=)
Diagnosis for which ZALTRAP was used (n, %)	
Colorectal cancer	
Other cancers	
Wet AMD	
Diabetic macular edema	
Other diagnoses	
Specialty of physician overseeing treatment (n, %)	
Ophthalmologist	
Oncologist	
Other physician specialties	
Treatment setting (n, %)	
Inpatient	
Outpatient	

11 APPENDICES

Appendix A. Diagnosis Codes For Cancer and Ophthalmic Diagnoses of Interest

Diagnosis	Description	ICD-10 Codes
Malignant colorectal cancer	Malignant neoplasm of colon	C18.x
Malignant colorectal cancer	Malignant neoplasm of rectum	C20.x
Malignant colorectal cancer	Malignant neoplasms of anus and anal canal	C21.x
Other Malignancies	Malignant neoplasms	C00.x – C17.0, C19.x, C22.x – C97.x
Other Malignancies	In-situ neoplasms	D00.x - D09.x
Other Malignancies	Benign neoplasms	D10.x - D36.x
Other Malignancies	Neoplasms of uncertain or unknown behavior	D37.x - D48.x
Wet age-related macular degeneration	Degeneration of macula and posterior pole	H35.3
Diabetic macular edema	Other specified retinal disorders	H35.8
Diabetic macular edema	Insulin-dependent diabetes mellitus with ophthalmic complications	E10.3
Diabetic macular edema	Non-insulin-dependent diabetes mellitus with ophthalmic complications	E11.3

Appendix B. List of Targeted Agents Approved for mCRC in the EU Other Than Aflibercept (ZALTRAP)

Drug Name
Cetuximab
Bevacizumab
Panitumumab