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Safety outcomes of low versus high dose imatinib mesylate in patients with advanced, metastatic, or nonresectable gastrointestinal stromal tumors: A systematic review

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Abstract

Background and Objectives: Gastrointestinal stromal tumors (GIST) are a rare cancer where tumors grow along the gastrointestinal tract. While treatment options aim towards surgical resection, some patients present with advanced metastatic and/or nonresectable diseases. The tyrosine kinase inhibitor imatinib mesylate is approved for this indication. However, dose escalation from 400 to 600 mg/d or 800 mg/d is allowed. The present study systematically evaluates the safety outcomes, particularly the incidence of grade ⩾ 3 adverse events (AEs) with low dose compared with high dose imatinib in these patients.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines were utilized to identify relevant studies through the PubMed, Cochrane Library, and Ovid databases and included randomized and non-randomized clinical trials comparing a low dose intervention of imatinib 400 mg/d with a high dose comparator of 600 or 800 mg/d in patients with histologically confirmed advanced metastatic and/or nonresectable GIST. Four studies were reviewed regarding study summaries and patient characteristics, patient demographics, and risk of bias, with a main emphasis on the evaluation of both efficacy outcomes and safety outcomes.

Results: Three of the four studies did not provide significant differences in response outcomes; however, all four studies reported a higher incidence of grade ⩾ 3 AEs in the high dose imatinib groups. Individual study reports of more high dose patients experiencing a grade ⩾ 3 event ranged from 0.6% to 19.8%, while combined low and high dose patient arms revealed a 17.1% difference favoring a high dose patient event. A sub-analysis of the three most frequently occurring categories, blood and lymphatic system disorders, gastrointestinal disorders, and general

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Conflicts of interest

All authors declare that they do not have any competing interests.

disorders and administration site conditions each revealed more high dose patients experiencing said category events compared to those low dose counterparts.

Conclusion: Low dose imatinib provides clinically meaningful response and demonstrated better tolerability with less frequently reported reactions. This evidence supports further research into the maintenance of 400 mg/d for this patient population compared to a dose escalation.

Keywords

gastrointestinal stromal tumors; imatinib; dosage; metastatic and nonresectable diseases

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are a rare type of cancer where abnormal cells grow along the tissues of the gastrointestinal tract, including organs such as the stomach, small and large intestine.[1] GISTs do not have the same pathology as other gastrointestinal (GI) cancers and require different treatments and management. GISTs are rare with reported global incidence rates of 10 to 22 per million annually.[2,3] Symptoms may be acute or chronic depending on the tumor size, site, and aggressiveness of the disease.[1,4] While most patients affected with GISTs are over the age of 50, rare diagnoses occur in individuals less than 20 years of age.[4,5] Management and treatment of GISTs depend on the extensiveness of the disease, with a particular focus on how much the disease metastasized. Primary treatment for localized disease is surgical resection with adjuvant therapy of a tyrosine kinase inhibitor (TKI), imatinib.[1,4,5] However, GISTs do not always respond well to radiotherapy and chemotherapy, and not all patients have resectable or localized disease.

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (CPGs), the first line of therapy is neoadjuvant imatinib for patients with unresectable, recurrent, or metastatic GIST to reduce tumor size.[5] Subsequently, if patents demonstrate a response or stable disease, imatinib is continued and surgery is performed when feasible. In the instances of progression, imatinib at 400 mg/d can be continued, imatinib can be escalated to 800 mg/d, or patients can switch to a different TKI. According to EBSCO, the CPGs also recommend imatinib treatment and evaluation of response to determine if surgery is feasible.[4] When disease remains nonresectable, imatinib is continued indefinitely or until there is no longer clinical benefit. When disease progression is observed, a dose escalation to 800 mg/d is considered as well as switching TKIs.

This review focuses on the intervention imatinib mesylate, a TKI originally approved in 2001, with accelerated approval a year later for advanced or metastatic GIST. Imatinib blocks the abnormal proteins from signaling cancer cells to multiply and spread.[6–8] The intervention and comparator used in this review are both imatinib, but administered at different doses. The intervention is administered at 400 mg/d while the comparator is administered at 600 mg/d or 800 mg/d. The goal with imatinib is to provide a response meaningful enough for resection or stable disease. Median survival with imatinib in patients with primary disease is 13.6 years, but patients with metastatic disease have a median survival of 6.4 years.[9] The most frequently occurring adverse events (AEs) associated with imatinib include edema, nausea, vomiting, diarrhea, abdominal pain and muscle cramps.[8]

It is important to investigate the difference in safety outcomes between low and high dose imatinib as both can be administered for this population, with considerations. Efficacy outcomes are typically the primary endpoints evaluated for dose comparison studies to determine the most effective dose with therapeutic benefit, in order for a drug to gain approval. As a result, safety parameters receive less attention.[10] However, the need to review safety outcomes is equally as important so researchers and medical professionals can gain a comprehensive understanding of how a drug interacts with patients. Evaluating safety outcomes during the drug development process, particular during clinical trials, helps researchers understand the incidence and prevalence of reactions as well as the pharmacokinetics of the drug.

A systematic review presented an overview of the efficacy on various biological treatment interventions in different patient populations with GIST.[11] Specific to the patient population and intervention discussed in this review, the efficacy outcomes revealed higher or longer overall response rate (ORR) and overall survival (OS) rates in the 800 mg/d (high dose) cohort. However, these outcomes were not statistically significant.[11] Additionally, one study was not sufficiently powered to determine the superior dose level and only one study demonstrated statistical significance with progression free survival (PFS) for the 800 mg/d group.[11] As demonstrated with existing reviews and publications, the efficacy of this intervention and patient population is already established; therefore, this review will address the missing safety outcome component to provide additional considerations when comparing different doses of the same drug.

Executing on high-level safety outcome initiatives has proven to be a difficult task for a multitude of reasons. These include: a universally acceptable standard for determining if an event represents a true risk or a false-positive not existing, leading to certain datapoints open to interpretation; randomized controlled trials not usually powered to detect harm; and inconsistencies in how researchers report AEs in clinical trials.[10] These inconsistencies include misclassification, incorrect relatedness assessments, and missed opportunities to gather event information.

METHODS

A review protocol for this systematic review has not been previously reported on the International Prospective Register of Systematic Reviews (PROSPERO).[12]

The following population, intervention, comparison, outcome (PICO) question was formulated and utilized for the analysis of this review: Among patients with advanced, metastatic or nonresectable gastrointestinal stromal tumors (GISTs) [P], how does low dose imatinib treatment of 400 mg/d [I] compare to high dose imatinib treatment of 600 mg/d or 800 mg/d [C], in bringing about the prevalence of grade ⩾ 3 adverse events [O]?

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) was used as the framework for writing this systematic review.[13]

Eligibility criteria

Clinical trials investigating low dose imatinib versus high dose imatinib in patients with metastatic, advanced or unresectable GIST were selected. For this systematic review, study inclusion criteria were (1) clinical trials (Phase II and III, randomized/non-randomized, and controlled/noncontrolled); (2) an intervention of 400 mg/d of imatinib; (3) a comparator of either 600 mg/d or 800 mg/d of imatinib; (4) patients who are ages ⩾ 18 years with no age limit; (5) patients with histologically confirmed, metastatic, advanced or unresectable GIST; (6) studies with a sample size of at least 10 individuals on each study arm; (7) a study dropout rate < 20%; (8) studies conducted from 1990 to present; and (9) studies published in English.

For this systematic review, study exclusion criteria were: (1) non-clinical trials including observational and cohort studies; (2) study comparator being a placebo or a dose lower than 400 mg/d; (3) patients with comorbidities, chemotherapy or biologic therapy or interventional drug treatment within 28 days of study entry, major surgery within 14 days of study entry, a life expectancy < 6 months, and severe concomitant disease; (4) studies that did not confirm patient diagnosis prior to enrollment; (5) studies with a sample size of < 10 individuals on each study arm; (6) a study dropout rate of > 20%; (7) studies conducted prior to 1990; and (8) studies reported in non-English languages.

Search strategy and study selection

The initial literature search was conducted in February 2023. In total, 1,500 articles were identified when searching the PubMed, Cochrane Library, and Ovid databases using a variety of keywords and medical patient headings (MeSH) in reference to Gastrointestinal Stromal Tumors, Imatinib Mesylate, and Drug-Related Side Effects and Adverse Reactions. The final search syntax aligning with the above stated PICO question was conducted on July 16, 2023 is listed below:

1. Gastrointestinal stromal tumors OR gastrointestinal stromal neoplasm OR gastrointestinal stromal neoplasms OR gastrointestinal stromal sarcoma OR gastrointestinal stromal tumor OR GIST OR GISTs;
2. Imatinib mesylate Alpha-(4-methyl-1-piperazinyl)-3’-((4-(3-pyridyl)-2-pyrimidinyl)amino)-p-tolu-p-toluidide OR CGP57148 OR CGP57148B OR Gleevec OR Glivec OR Imatinib OR Imatinib methanesulfonate OR ST1571 OR STI571;
3. 1 AND 2;
4. Imatinib mesylate Alpha-(4-methyl-1-piperazinyl)-3’-((4-(3-pyridyl)-2-pyrimidinyl)amino)-p-tolu-p-toluidide OR CGP57148 OR CGP57148B OR Gleevec OR Glivec OR Imatinib OR Imatinib methanesulfonate OR ST1571 OR STI571;
5. 3 AND 4;
6. Drug-Related Side Effects and Adverse Reactions OR adverse drug event OR adverse drug reaction OR drug side effects OR drug toxicity OR drug-related

side effects and adverse reaction OR side effects of drugs OR toxicity, drugs OR adverse event OR serious adverse event OR ADE OR ADR OR AE OR SAE;

7. 5 AND 6.

Due to the specificity of the intervention and comparator items, pearl growing techniques were utilized to ensure all relevant articles were captured.[14] All three databases were searched. However, no additional articles were identified. Of the 1,500 articles that were identified, a total of 278 were removed as duplicates before screening. Of the remaining 1,222 records screened by their title and abstract, 1,190 were excluded for various reasons including comparing imatinib to a placebo, investigating other drugs in the target population, and focusing on different indications. Of the remaining 32 records sought for retrieval, 7 could not be retrieved. Twenty-five reports were assessed for eligibility and 21 were excluded for reasons including not reporting safety data or outcomes ($n = 7$), not meeting the inclusion criteria ($n = 5$), not reporting on a clinical trial but serving as a protocol or approval summary ($n = 8$), and not written in the English language ($n = 1$). The remaining 4 articles were included in this review for analysis and discussion purposes. This selection process was conducted by one author and articles were sorted manually without assistance from automation tools. Articles were imported from the aforementioned databases and stored in EndNote software. A PRISMA flow diagram outlining the search process is provided in Figure 1.

Data collection

An Excel spreadsheet was utilized to track studies, collect data, perform analyses, and gather applicable data related to the PICO question. No automation tools were used to facilitate data collection.

All four studies presented safety data with a table, comparing each study arm to the total number of subjects.[15–18] One article presented the number of events for each Common Toxicity Criteria (CTC) v2.0 major event (*i.e.*, gastrointestinal),[15] two articles presented data based on specific events (*i.e.*, nausea)[16,18] and one presented both major CTC events and specific events.[17] All data presented in each of the articles was extracted as reported, compiled, and re-organized based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. To further examine studies that only reported major event data, a search for Supplemental Tables was conducted. However, no additional information was discovered.

The Cochrane Risk of Bias (ROB) tool was used to evaluate the risk of bias in the four evaluated studies.[19] Seven domains were evaluated and each was given a score of Low Risk, High Risk, or Unclear Risk. An overall quality score was assigned for each study based on the number of high risk of bias and low risk of bias scores. Studies with five or more high risk scores were marked poor quality, 2–5 high risk scores were marked moderate quality, and < 2 high risk scores were marked good quality.

Outcomes

The primary outcome measured through this systematic review was safety and tolerability, comparing low dose and high dose imatinib, focusing on the occurrence of grade ⩾ 3

AEs. These outcomes are identified as major CTCAE category safety outcomes and specific individual safety event outcomes that fall under the major categories.

Data analysis

Each of the four articles included in this systematic review graded safety events with the CTC v2.0. While this was the applicable grading system at the time each article was published, this systematic review updated the historic data to align with the current classification system utilizing the CTCAE v5.0. The CTCAE provides descriptive terminology for AE reporting as well as a severity grading scale for each event listed within each category. This comprehensive toolkit contains 26 categories and groups categories by system organ class (SOC) as the highest level of hierarchy (identified by anatomy or physiological system, etiology, or purpose) and then specific AEs within the SOC with a severity grade. The grading scale for the severity of events is listed below:

1. Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated;
2. Moderate; minimal, local or noninvasive intervention; limiting age-appropriate instrumental ADL (activities of daily living);
3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;
4. Life-threatening consequences; urgent intervention indicated;
5. Death related to AEs.

Given that the original reported data was classified under the CTC v2.0 and converted into the active CTCAE v5.0, it was expected that some category events would not fit into current classifications. The four instances where this occurred and the actions taken are noted below:

1. In CTC v2.0 the Hemorrhage category contained various events non-specific to a body part or organ function. CTCAE v5.0 eliminated the Hemorrhage category and placed specific hemorrhage events under new SOC. Identifiable hemorrhage events were mapped accordingly. However, non-specific hemorrhage events that could not be re-categorized because the event was not specified remained under the original Hemorrhage category for the full dataset analysis.
2. The above also applies to the Syndromes category.
3. In CTC v2.0 the category Infection/Febrile Neutropenia was grouped together. In CTCAE v5.0 these events were re-mapped under the specific event of “Febrile Neutropenia” which falls under the Blood and Lymphatic System Disorders SOC.
4. The following specific laboratory events were added to the Blood and Lymphatic System Disorders SOC: neutropenia, leukopenia, granulocytopenia and thrombocytopenia.

When the original articles did not provide major category or individual event information, “Not Reported” was utilized in the Results tables. A “Specific Event Not Reported” row was added to account for when major category events occurred but were not specified. Available data was utilized to conduct data analyses. If there were no reported events for major categories, “No Data to Analyze” was utilized for the data analysis row.

A sub-analysis table was created for blood and lymphatic system disorders, gastrointestinal disorders, and general disorders and administration site conditions and is included in the results section for closer examination. Descriptive analyses were performed on the data including intra-article analysis for each major CTCAE category outcome for each of the four articles. In addition, a summation of all low dose arm and all high-dose arm patients was calculated to conduct a complete analysis for each major category outcome.

RESULTS

Study summary

The four evaluated studies included three randomized trials and one non-randomized trial (Table 1).[15–18] All studies utilized 400 mg/d imatinib as the low dose intervention. Two studies used 800 mg/d imatinib as the high dose comparator,[15,18] while the other two used 600 mg/d as the high dose comparator.[16,17] Each study included individuals with metastatic or nonresectable GIST. Efficacy outcomes included PFS, OS, and ORR, while safety outcomes were measured with CTC v2.0.

Patient characteristics

Patient characteristics between the four studies showed similarities in terms of age, sex, primary site of the tumor, and previous treatment (Table 2). Age ranges included 18 years up to 94 years of age with a median age range of 54 to 61.1 years. Most patients had a gastrointestinal primary tumor and surgery was the most common previous treatment for all studies with data. Additionally, many patients underwent more than one previous treatment. Individual studies were well balanced and had comparable baseline characteristics between intervention and comparator arms. One study did not provide data for each arm but for the study as a whole.[16]

Risk of bias

Risk of bias was assessed for the four studies included in this review using the Cochrane ROB tool (Table 3).[19] Selection bias regarding random sequence generation was marked low risk for three of the four studies as they utilized various random components including a dynamic balancing algorithm program, block randomization, and central randomization with minimization technqiues.[15,16,18] One study was non-randomized and all subjects recruited after a certain date were allocated to the comparator arm, resulting in a high selection bias for both randomization and allocation concealment.[17] The other study evaluated with a high selection bias (allocation concealment) did not mask their allocation.[18] All four studies scored low in performance bias and detection bias.[15–18] While they were open-label, it did not influence outcome measurements from blinding or allocation. Each study also had a low risk for attrition bias regarding the amount, reason, or handling of incomplete

outcomes. Lastly, reporting bias was low risk for each study as they included expected outcomes and the primary and secondary outcomes were reported. It is important to note that other bias detected was in regards to response evaluation. As one study noted, RECIST criteria is not the best criteria to use for evaluation, as responsive GISTs that become cystic enlarge, which classifies as progressive disease.[15] This can result in objective response rates appearing artifactually low.

Study outcomes

For each of the four studies, more high dose patients experienced a grade ⩾ 3 AE, with percentages ranging from 0.6% to 19.8%.[15–18] An overall combined patient analysis determined that 329 (36%) of all low dose patients (n = 915) and 499 (53%) of all high dose patients (n = 939) experienced a grade ⩾ 3 AE, a 17.1% difference. A full analysis of all CTCAE categories and the two additional categories resulted in 28 major categories evaluated and an intra-study comparison for each study. Of these 112 datapoints (28 categories x 4 studies), 29 (25.9%) yielded more high dose patients experiencing an event, 67 (59.8%) did not have reported data, 8 (7.1%) yielded more low dose patients experiencing an event, and 8 (7.1%) had no difference between arms.

However, 11 CTCAE SOCs did not report an event in any of the four studies: congenital, familial and genetic disorders; endocrine disorders; infections and infestations; injury, poisoning and procedural complications; investigations; pregnancy, puerperium and perinatal conditions; psychiatric disorders; reproductive system and breast disorders; social circumstances; surgical and medical procedures; and vascular disorders. Excluding these SOCs resulted in a total of 17 SOCs evaluated and an intra-study comparison of 68 datapoints. Of these 68 evaluations, 29 (42.6%) yielded more high dose patients experiencing an event, 23 (33.8%) did not have reported data, 8 (11.8%) yielded more low dose patients experiencing an event, and 8 (11.8%) had no difference between arms.

The total patient analysis of the 17 SOCs resulted in 16 (94.1%) categories of more high dose patients experiencing an event and 1 (5.9%) category more low dose patients experiencing an event. For the 1 SOC where low dose events were higher (eye disorders), the percentage was only 0.1%. The instances where more total high dose patients experienced an event ranged from 0.1% to 10.8%. (Table 4).

Sub-analysis

A sub-analysis was conducted for the Blood and Lymphatic System Disorders, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions SOCs as they were the three SOCs with the most reported events (Table 5).

Blood and lymphatic system disorders: Three of the four studies intra-analysis resulted in more high dose patients experiencing a blood and lymphatic system disorders event.[15,17,18] The total analysis for this SOC yielded 10.8% more high dose patients experiencing an event compared to the low dose group. Of the total low dose (n = 205) and high dose (n = 312) patients experiencing a specific event, anemia was the most frequently

occurring event for both low dose (71 (34.6%)) and high dose patients (136 (43.6%)) (Table 5).

Gastrointestinal disorders: Two of the four studies in the intra-analysis resulted in more high dose patients experiencing a Gastrointestinal Disorders event.[15,18] The total analysis for this SOC yielded 4.4% more high dose patients experiencing an event compared to the low dose group. Of the total low dose (n = 80) and high dose (n = 123) patients experiencing a specific event, nausea and vomiting were the most common events for low dose patients (14 (17.5%)), and diarrhea was the most common event for high dose patients (29 (23.6%)). A majority of the Gastrointestinal events were not specifically reported resulting in unknown events for both low dose (31 (38.8%)) and high dose (54 (43.9%)) groups. (Table 5).

General disorders and administration site conditions: Three of the four studies intra-analysis resulted in more high dose patients experiencing a General Disorders and Administration Site Conditions event.[15,17,18] The total analysis for this SOC yielded 9.1% more high dose patients experiencing an event compared to the low dose group. Of the total low dose (n = 95) and high dose (n = 183) patients experiencing a specific event, fatigue was the most common event for both low dose (29 (30.5%)) and high dose patients (52 (28.4%)). (Table 5).

Deaths

In the CTCAE v5.0, deaths are classified as a grade 5. Since this review focuses on grade ⩾ 3 AEs, an additional analysis was conducted for patient deaths. In Blanke *et al.*, 2 low dose patients (0.6%) and 9 high dose patients (2.6%) experienced possible treatment-related deaths. Four of the high dose patient deaths were caused from gastrointestinal bleeding. The remaining deaths were from cerebrovascular ischemia, shortness of breath and bronchitis, infection combined with arrhythmia, liver failure, and confusion. Two other unspecified deaths could not be ruled out as treatment related.[15] In Demetri *et al.*, 9 low dose patients (12.3%) and 5 high dose patients (6.8%) died.[16] In Nishida *et al.*, disease progression during treatment occurred in 48 patients. Two patients died during the trial, and a follow-up of discontinued patients revealed 20 additional patient deaths. Since these deaths were not linked to a dose, a sub-analysis could not be conducted.[17] In Verweij *et al.*, imatinib was the most probable cause of death in 5 (0.5%) patients; 2 low dose patients and 3 high dose patients. For 13 (1%) other deaths, imatinib could not be completely ruled out. Hepatic toxic effects (n = 3) and bleeding (n = 2) were linked to 5 deaths.[18]

DISCUSSION

All four studies support the effectiveness of imatinib administration as the standard of care for patients with advanced, metastatic, or nonresectable GIST.[15–18] Imatinib was generally well tolerated with both low dose and high dose patients. However, therapy was better tolerated within the low dose arms and total low dose patients.

It is important to first highlight efficacy, although not a major focus of this paper, to better understand the comparison of how the low dose and high dose arms compare. Three of the four studies did not produce significant differences between two groups for PFS, OS,

or ORR.[15–17] One study that measured both OS and PFS observed statistical significance with PFS on the high dose arm, but no statistical significance with OS between the two arms.[18] This aligns with the previously mentioned clinical practice guidelines to initiate treatment at 400 mg/d and maintain until surgery is viable, or consider dose escalation if disease progression is observed.

These efficacy outcomes were further explained in a systematic review detailing different biological interventions for different patient populations with GIST.[11] Higher dosing of imatinib at 800 mg/d may provide longer or higher outcomes for patients, but said review did not address the safety and tolerability outcomes of each of the reviewed publications. As a result, the need to establish research and report on safety outcomes was critical.[11]

Regarding safety outcomes, all four studies revealed more high dose patients experiencing a grade ⩾ 3 AE than their low dose counterparts. These frequencies ranged from a 0.6% to 19.8% higher chance of occurrence. In addition to a higher frequency of Grade ⩾ 3 AE experienced on the high dose imatinib, there were more CTC SOC events observed on either the 600 mg/d or 800 mg/d dose. Regardless of the dose, blood and lymphatic system disorders, gastrointestinal disorders, and general disorders and administration site conditions events were the most common and should be monitored closely throughout treatment. While some articles did not specify the cause of death and it would be anticipated to see higher death rates for the high dose patients, it could be considered that low dose patients experienced progressive-disease related deaths. This evaluation further stresses the need for more research into safety outcomes, highlighted by the gap in specificity of reported outcomes.

There were limitations to this review including the frequency of reported safety outcomes by each individual author. Two articles reported data for the number of patients who started treatment[15,18] and the remaining articles reported data for events that occurred in at least 5% and 10% of patients in at least one arm.[16,17] While this review synthesized available data, the impact of excluded events that occurred in < 5% and < 10% of patients is unknown.

Another limitation was the specifics of shared data from each article. Not all sub-analyses could be conducted because some articles only reported the category events and not the specific events. However, this did not prevent an analysis of the available data. Additionally, statistical significance was not calculated for this review. Instead, data frequencies and percent calculations were performed by comparing the low dose and high dose arms.

While high dose imatinib may have provided slightly better efficacy outcomes, many were not statistically superior than low dose imatinib and there were numerous safety outcome measures that favored low dose tolerability. Based on this review, the evidence supports additional research into the initial recommended dose of 400 mg/d for this patient population, as it provides meaningful PFS, OS, and ORR outcomes, while being less toxic than a higher dose. These findings are especially relevant with the new initiative from the FDA, Project Optimus, focused on a dose-discovery and a dose optimization in oncological drug development.[20,21] This change shifts from the maximum tolerated dose (MTD)

model and towards an optimal dose-response for favorable efficacy and safety/tolerability outcomes.[20,21]

Low dose imatinib provides clinically meaningful efficacy outcomes with fewer reported AEs. These results support additional research into the circumstances of high dose imatinib dosing as well as an assessment of the risk/benefit ratio.

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Data sharing statement

Availability of data, code, and other materials is not publicly available.

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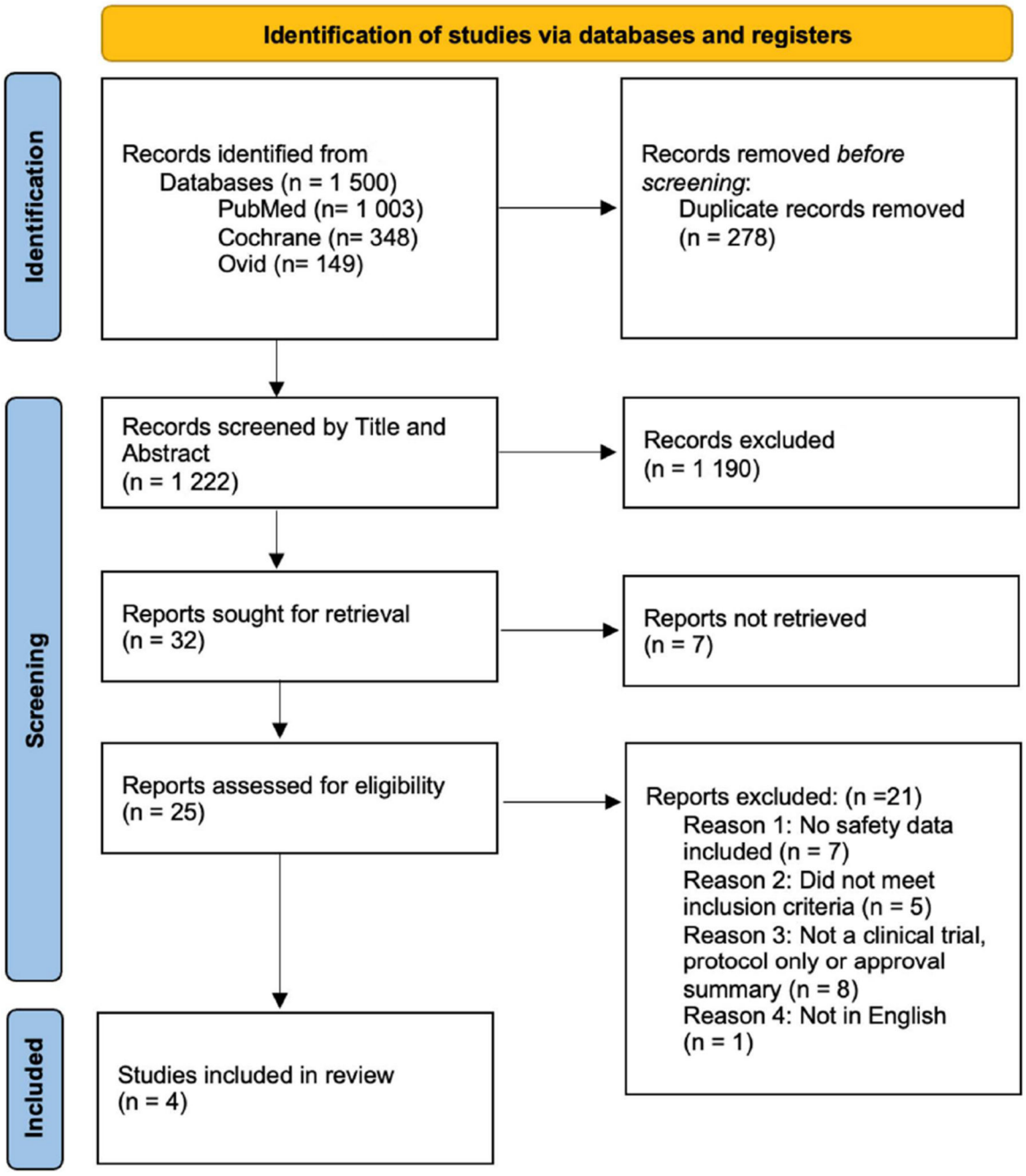

Figure 1.
PRISMA flow diagram.

Table 1:

Study summary and characteristics

Study	Year	Location	Diagnosis	Intervention	Comparator	Primary outcome	Primary outcome measurement	Safety outcome	Safety outcome measurement
Blanke *et al.*[15] (Citation 1)	2008	USA, Canada, Puerto Rico	Metastatic or non-resectable GIST	400 mg/d imatinib	800 mg/d imatinib	PFS and OS	RECIST 1.0	Toxicities	NCI-CTC, version 2.0
Demetri *et al.*[16] (Citation 2)	2002	USA, Australia, Finland	Metastatic or non-resectable GIST	400 mg/d imatinib	600 mg/d imatinib	ORR	Southwest Oncology Group criteria	Safety and tolerability	NCI-CTC, version 2.0
Nishida *et al.*[17] (Citation 3)	2008	Japan	Metastatic or non-resectable GIST	400 mg/d imatinib	600 mg/d imatinib	ORR	Southwest Oncology Group criteria	Toxic effects	NCI-CTC, version 2.0
Verweij *et al.*[18] (Citation 4)	2004	Belgium, Switzerland, France, Germany, Australia, Italy, Netherlands, Poland, United Kingdom, New Zealand, Spain, Denmark, Singapore	Advanced, metastatic or non-resectable GIST	400 mg/d imatinib	800 mg/d imatinib	PFS	RECIST 1.0	Toxic effects	NCI-CTC, version 2.0

NCI-CTC: The National Cancer Institute Common Toxicity Criteria (today referred to as the Common Terminology Criteria for Adverse Events (CTCAE)); PFS: progression free survival; ORR: overall response rate; OS: overall survival

Table 2:

Patient characteristics

Total number of patients		Blanke *et al.* (Citation 1)		Demetri *et al.* (Citation 2)		Nishida *et al.* (Citation 3)		Verweij *et al.* (Citation 4)	
		400 mg/d (*n* = 345)	**800 mg/d (*n* = 349)**	**400 mg/d (*n* = 73)**	**600 mg/d (*n* = 74)**	**400 mg/d (*n* = 28)**	**600 mg/d (*n* = 46)**	**400 mg/d (*n* = 473)**	**800 mg/d (*n* = 473)**
Age (year)	Median	61.9	61.5	54		54	56.5	59	60
	Range	18–87	18–94	18–83		24–70	33–74	18–91	18–86
Sex, *n* (%)	Male	187 (54)	189 (54)	44 (60)	39 (53)	19 (68)	29 (63)	283 (60)	290 (61)
	Female	158 (46)	160 (46)	29 (40)	35 (47)	9 (32)	17 (37)	190 (40)	183 (39)
Primary site of the tumor, *n* (%)	Gastrointestinal	245 (71)	241 (69)	122 (83)				403 (85.2)	390 (82.5)
	Gastric/stomach	129 (37.4)	124 (35.5)	50 (34)				159 (33.6)	157 (33.2)
	Small bowel	103 (29.9)	109 (31.2)	72 (49)				177 (37.4)	150 (31.7)
	Abdomen	78 (22.6)	84 (24.1)	36 (24.5)				58 (12.3)	71 (15)
	Other GI	13 (3.8)	8 (2.3)	0 (0)				67 (14.2)	83 (17.5)
	Nonabdominal or GI	22 (6.4)	24 (6.9)	25 (17)				12 (2.5)	12 (2.5)
Previous treatment, *n* (%)	Surgery			144 (98)		25 (89.3)	42 (91.3)	410 (86.7)	392 (82.9)
	Chemotherapy			75 (51)		8 (28.6)	12 (26)	156 (33)	155 (32.8)
	Radiotherapy			22 (15)		0 (0)	0 (0)	26 (5.5)	37 (7.8)

Numbers reflect patients allocated at the time of study entry.

Table 3:

Risk of bias

Study	Year	Selection bias: random sequence generation	Selection bias: allocation concealment	Performance bias: blinding of participants	Detection bias: blinding outcome assessment	Attrition bias: incomplete outcome assessment	Reporting bias: selective reporting	Other bias	Overall quality
Blanke *et al.*	2008	L	L	L	L	L	L	Response Evaluation	GQ
Demetri *et al.*	2002	L	L	L	L	L	L	Response Evaluation	GQ
Nishida *et al.*	2008	H	H	L	L	L	L	Response Evaluation	MQ
Verweij *et al.*	2004	L	H	L	L	L	L	Response Evaluation	GQ

GQ: good quality; H: high risk of bias; L: low risk of bias; MQ: moderate quality

Table 4:

Study outcomes

	Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
	400 mg/d *n* = 344	**800 mg/d *n* = 347**	**400 mg/d *n* = 73**	**600 mg/d *n* = 74**	**400 mg/d *n* = 28**	**600 mg/d *n* = 46**	**400 mg/d *n* = 470**	**800 mg/d *n* = 472**	***n* = 915**	***n* = 939**
Number of patients experienced a grade ⩾ 3 AEs	149 (43.3%)	219 (63.1%)	15 (20.5%)	16 (21.1%)	13 (46.4%)	27 (58.7%)	152 (32.3%)	237 (50.2%)	329 (36%)	499 (53.1%)
	19.8% more HPD experienced a grade ⩾ 3 AEs		0.6% more HDP experienced a grade ⩾ 3 AEs		12.3% more HDP experienced a grade ⩾ 3 AEs		17.7% more HDP experienced a grade ⩾ 3 AEs		17.1% more HDP experienced a grade ⩾ 3 AEs	
Deaths	2 (0.6%)	9 (2.6%)	9 (12.3%)	5 (6.8%)	2		2 (0.4%)	3 (0.6%)	13 (1.4%)	17 (1.8%)
	2% more HDP experienced a death		5.5% more LDP experienced a death		No data to analyze		0.2% more HDP experienced a death		0.4% more HDP experienced a death	
Blood and lymphatic System disorders	83 (24.1%)	115 (33.1%)	8 (11%)	4 (5.4%)	15 (53.6%)	41 (89.1%)	99 (21.1%)	152 (32.2%)	205 (22.4%)	312 (33.2%)
	9% more HDP experienced an event		5.6% more LDP experienced an event		35.5% more HDP experienced an event		11.1% more HDP experienced an event		10.8% more HDP experienced an event	
Cardiac disorders	23 (6.7%)	48 (13.8%)	NR	NR	NR	NR	NR	NR	23 (2.5%)	48 (5.1%)
	7.1% more HDP experienced an event		No data to analyze		No data to analyze		No data to analyze		2.6% more HDP experienced an event	
Congenital, familial and genetic disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Ear and labyrinth disorders	0 (0%)	1 (0.3%)	NR	NR	NR	NR	NR	NR	0 (0%)	1 (0.1%)
	0.3% more HDP experienced an event		No data to analyze		No data to analyze		No data to analyze		0.1% more HDP experienced an event	
Endocrine disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Eye disorders	NR	NR	0 (0%)	0 (0%)	1 (3.6%)	0 (0%)	NR	NR	1 (0.1%)	0 (0%)
	No data to analyze		No difference between arms		3.6% more LDP experienced an event		No data to analyze		0.1% more LDP experienced an event	
Gastrointestinal disorders	31 (9%)	54 (15.6%)	6 (8.2%)	5 (6.8%)	5 (17.9%)	4 (8.7%)	38 (8.1%)	60 (12.7%)	80 (8.7%)	123 (13.1%)
	6.6% more HDP experienced an event		1.4% more LDP experienced an event		9.2% more LDP experienced an event		4.6% more HDP experienced an event		4.4% more HDP experienced an event	
General disorders and administration site conditions	41 (11.9%)	72 (20.7%)	2 (2.7%)	1 (1.4%)	6 (21.4%)	10 (21.7%)	46 (9.8%)	100 (21.2%)	95 (10.4%)	183 (19.5%)

	Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
	400 mg/d *n* = 344	**800 mg/d *n* = 347**	**400 mg/d *n* = 73**	**600 mg/d *n* = 74**	**400 mg/d *n* = 28**	**600 mg/d *n* = 46**	**400 mg/d *n* = 470**	**800 mg/d *n* = 472**	***n* = 915**	***n* = 939**
	8.8% more HDP experienced an event		1.3% more LDP experienced an event		0.3% more HDP experienced an event		11.4% more HDP experienced an event		9.1% more HDP experienced an event	
Hepatobiliary disorders	12 (3.5%)	13 (3.7%)	2 (2.7%)	2 (2.7%)	NR	NR	NR	NR	14 (1.5%)	15 (1.6%)
	0.2% more HDP experienced an event		No difference between arms		No data to analyze		No data to analyze		0.1% more HDP experienced an event	
Immune system disorders	0 (0%)	1 (0.3%)	NR	NR	NR	NR	NR	NR	0 (0%)	1 (0.1%)
	0.3% more HDP experienced an event		No data to analyze		No data to analyze		No data to analyze		0.1% more HDP experienced an event	
Infections and infestations	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Injury, poisoning and	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
procedural complications	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Investigations	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Metabolism and nutrition disorders	7 (2%)	10 (2.9%)	0 (0%)	0 (0%)	5 (17.9%)	5 (10.9%)	9 (1.9%)	8 (1.7%)	21 (2.3%)	23 (2.4%)
	0.9% more HDP experienced an event		No difference between arms		7% more LDP experienced an event		0.2% more LDP experienced an event		0.1% more HDP experienced an event	
Musculoskeletal and connective tissues disorders	2 (0.6%)	2 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	1 (0.2%)	9 (1.9%)	3 (0.3%)	12 (1.3%)
	No difference between arms		No difference between arms		2.2% more HDP experienced an event		1.7% more HDP experienced an event		1% more HDP experienced an event	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	NR	NR	1 (1.4%)	3 (4.1%)	NR	NR	NR	NR	1 (0.1%)	3 (0.3%)
	No data to analyze		2.7% more HDP experienced an event		No data to analyze		No data to analyze		0.2% more HDP experienced an event	
Nervous system disorders	12 (3.5%)	10 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)	6 (1.3%)	14 (1.5%)	16 (1.7%)
	0.6% more LDP experienced an event		No difference between arms		No difference between arms		0.9% more HDP experienced an event		0.2% more HDP experienced an event	

	Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
	400 mg/d *n* = 344	**800 mg/d *n* = 347**	**400 mg/d *n* = 73**	**600 mg/d *n* = 74**	**400 mg/d *n* = 28**	**600 mg/d *n* = 46**	**400 mg/d *n* = 470**	**800 mg/d *n* = 472**	***n* = 915**	***n* = 939**
Pregnancy, puerperium and perinatal conditions	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Psychiatric disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Renal and urinary disorders	3 (0.9%)	7 (2%)	NR	NR	NR	NR	3 (0.6%)	13 (2.6%)	6 (0.7%)	20 (2.1%)
	1.1% more HDP experienced an event		No data to analyze		No data to analyze		2% more HDP experienced an event		1.4% more HDP experienced an event	
Reproductive system and	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
breast disorders	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Respiratory, thoracic and mediastinal disorders	7 (2%)	13 (3.7%)	NR	NR	0 (0%)	1 (2.2%)	37 (7.9%)	56 (11.9%)	44 (4.8%)	70 (7.5%)
	1.7% more HDP experienced an event		No data to analyze		2.2% more HDP experienced an event		4% more HDP experienced an event		2.7% more HDP experienced an event	
Skin and subcutaneous tissue disorders	14 (4.1%)	26 (7.5%)	2 (2.7%)	2 (2.7%)	1 (3.6%)	11 (23.9%)	15 (3.2%)	32 (6.8%)	32 (3.5%)	71 (7.6%)
	3.4% more HDP experienced an event		No Difference Among Arms		20.3% more HDP experienced an event		3.6% more HDP experienced an event		4.1% more HDP experienced an event	
Social circumstances	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Surgical and medical procedures	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze
Vascular disorders	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No data to analyze		No data to analyze		No data to analyze		No data to analyze		No data to analyze	
Hemorrhage category	16 (4.7%)	38 (11%)	0 (0%)	3 (4.1%)	NR	NR	13 (2.8%)	38 (8.1%)	29 (3.2%)	79 (8.4%)
	6.3% more HDP experienced an event		4.1% more HDP experienced an event		No data to analyze		5.3% more HDP experienced an event		5.2% more HDP experienced an event	
Syndromes category	0 (0%)	1 (0.3%)	NR	NR	NR	NR	NR	NR	0 (0%)	1 (0.1%)

	Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
	400 mg/d *n* = 344	**800 mg/d *n* = 347**	**400 mg/d *n* = 73**	**600 mg/d *n* = 74**	**400 mg/d *n* = 28**	**600 mg/d *n* = 46**	**400 mg/d *n* = 470**	**800 mg/d *n* = 472**	***n* = 915**	***n* = 939**
	0.3% more HDP experienced an event		No data to analyze		No data to analyze		No data to analyze		0.1% more HDP experienced an event	

NR: not reported; HDP: high dose patients; LDP: low dose patients

Table 5:

Sub-analysis: Blood and lymphatic system disorders, gastrointestinal disorders, general disorders and administration site conditions

		Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
		400 mg/d (*n* = 344)	800 mg/d (*n* = 347)	400 mg/d (*n* = 73)	600 mg/d (*n* = 74)	400 mg/d (*n* = 28)	600 mg/d (*n* = 46)	400 mg/d (*n* = 470)	800 mg/d (*n* = 472)	(*n* = 915)	(*n* = 939)
Blood and lymphatic system disorders	**SOC TOTALS**	**83 (24.1%)**	**115 (33.1%)**	**8 (11%)**	**4 (5.4%)**	**15 (53.6%)**	**41 (89.1%)**	**99 (21.1%)**	**152 (32.2%)**	**205 (22.4%)**	**312 (33.2%)**
	Anemia	32 (38.6%)	47 (40.9%)	1 (12.5%)	2 (50%)	5 (33.3%)	8 (19.5%)	33 (33.3%)	79 (52%)	71 (34.6%)	136 (43.6%)
	Febrile Neutropenia	15 (18.1%)	23 (20%)	Not Reported	Not Reported	Not Reported	Not Reported	13 (13.1%)	22 (14.5%)	28 (13.7%)	45 (14.4%)
	Neutropenia	24 (28.9%)	34 (29.6%)	5 (62.5%)	2 (50%)	3 (20%)	13 (31.7%)	Not Reported	Not Reported	32 (15.6%)	49 (15.7%)
	Leukopenia	Not Reported	Not Reported	2 (25%)	0 (0%)	Not Reported	Not Reported	13 (13.1%)	12 (7.9%)	15 (7.3%)	12 (3.8%)
	Granulocytopenia	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	33 (33.3%)	33 (21.7%)	33 (16.1%)	33 (10.6%)
	Thrombocytopenia	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported	7 (7.1%)	6 (3.9%)	7 (3.4%)	6 (1.9%)
	Specific event not reported	12 (14.5%)	11 (9.6%)	0 (0%)	0 (0%)	7 (46.7%)	20 (48.8%)	0 (0%)	0 (0%)	19 (9.3%)	31 (9.9%)
Gastrointestinal disorders	**SOC TOTALS**	**31 (9%)**	**54 (15.6%)**	**6 (8.2%)**	**5 (6.8%)**	**5 (17.9%)**	**4 (8.7%)**	**38 (8.1%)**	**60 (12.7%)**	**80 (8.7%)**	**123 (13.1%)**
	Ascites	Not Reported	Not Reported	Not Reported	Not Reported	1 (20%)	0 (0%)	Not Reported	Not Reported	1 (1.3%)	0 (0%)
	Constipation	Not Reported	Not Reported	Not Reported	Not Reported	0 (0%)	0 (0%)	5 (13.2%)	7 (11.7%)	5 (6.3%)	7 (5.7%)
	Diarrhea	Not Reported	Not Reported	1 (16.7%)	2 (40%)	0 (0%)	2 (50%)	8 (21.1%)	25 (41.7%)	9 (11.3%)	29 (23.6%)
	Nausea	Not Reported	Not Reported	1 (16.7%)	1 (20%)	1 (20%)	1 (25%)	12 (31.6%)	15 (25%)	14 (17.5%)	17 (13.8%)
	Vomiting	Not Reported	Not Reported	0 (0%)	1 (20%)	1 (20%)	1 (25%)	13 (34.2%)	13 (21.7%)	14 (17.5%)	15 (12.2%)
	Upper GI tract bleeding or perforation	Not Reported	Not Reported	3 (50%)	1 (50%)	Not Reported	Not Reported	Not Reported	Not Reported	3 (3.8%)	1 (0.8%)
	Abdominal pain	Not Reported	Not Reported	1 (16.7%)	0 (0%)	2 (40%)	0 (0%)	Not Reported	Not Reported	3 (3.8%)	0 (0%)

		Citation 1		Citation 2		Citation 3		Citation 4		Total low dose patients	Total high dose patients
		400 mg/d (*n* = 344)	**800 mg/d (*n* = 347)**	**400 mg/d (*n* = 73)**	**600 mg/d (*n* = 74)**	**400 mg/d (*n* = 28)**	**600 mg/d (*n* = 46)**	**400 mg/d (*n* = 470)**	**800 mg/d (*n* = 472)**	**(*n* = 915)**	**(*n* = 939)**
	Specific event not reported	31 (100%)	54 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	31 (38.8%)	54 (43.9%)
General disorders and administration site conditions	**SOC TOTALS**	**41 (11.9%)**	**72 (20.7%)**	**2 (2.7%)**	**1 (1.4%)**	**6 (21.4%)**	**10 (21.7%)**	**46 (9.8%)**	**100 (21.2%)**	**95 (10.4%)**	**183 (19.5%)**
	Fatigue	Not Reported	Not Reported	0 (0%)	0 (0%)	1 (16.7%)	1 (10%)	28 (60.9%)	51 (51%)	29 (30.5%)	52 (28.4%)
	Malaise	Not Reported	Not Reported	Not Reported	Not Reported	0 (0%)	1 (10%)	Not Reported	Not Reported	0 (0%)	1 (0.5%)
	Pyrexia (fever)	Not Reported	Not Reported	Not Reported	Not Reported	1 (16.7%)	0 (0%)	4 (8.7%)	6 (6%)	5 (5.3%)	6 (3.3%)
	Edema limbs	Not Reported	Not Reported	0 (0%)	0 (0%)	0 (0%)	1 (10%)	Not Reported	Not Reported	0 (0%)	1 (0.5%)
	Edema face	Not Reported	Not Reported	1 (50%)	0 (0%)	1 (16.7%)	1 (10%)	Not Reported	Not Reported	2 (2.1%)	1 (0.5%)
	Pain	27 (65.9%)	42 (58.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (28.4%)	42 (23%)
	Specific event not reported	14 (34.1%)	30 (41.7%)	1 (50%)	1 (100%)	3 (50%)	6 (60%)	14 (30.4%)	43 (43%)	32 (33.7%)	80 (43.7%)

SOC: system organ class