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# RETROSPECTIVE SAFETY EVALUATION OF TYROSINE KINASE INHIBITOR PRODUCTS WHEN ADMINISTERED IN SINGLE DOSE IN CROSSOVER STUDIES TO HEALTHY VOLUNTEERS


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## PURPOSE

Tyrosine Kinases (TKs) have emerged as major targets of drug discovery in precision oncology. Tyrosine Kinase Inhibitors (TKIs) are multi-targeted anticancer drugs that inhibit tyrosine kinases involved in tumorigenesis, tumor progression, and metastatic progression. Since the approval of the first TKI by the Food and Drug Administration (FDA) in 2001, some clinical challenges have emerged including important toxicity profiles of certain TKIs. This raises safety concerns for the patients who are chronic users of TKIs but also for healthy volunteers (HVs) who are administered TKIs for clinical trials, whether in the context of new investigational product (IP) or bioequivalence (BE, generic investigational product) studies. Regulatory Agency requirements to conduct BE studies with TKIs are not always concordant in terms of design and study population. Our Contract Research Organization (Altasciences) has gained considerable experience in conducting BE studies with different TKIs since 2010 in HVs.

**We aimed to perform a retrospective evaluation of the safety profile of these studies to support and facilitate the conduct of different phase I studies with TKIs in HVs.**

## INTRODUCTION

- TKs trigger the activation of signaling cascades and act as key regulators of cell survival and proliferation. The abnormal activation of TKs is implicated in tumorigenesis, tumor growth, and metastasis.[1,2] TKs have therefore emerged as important targets for cancer therapy (**Figure 1**). The first TKI approved by the FDA in 2001 was imatinib, and since then, over 50 TKIs have been marketed and occupy an important place in precision oncology treatments.[2,3]
- Over the past decades, studies have reported that TKIs are generally better tolerated than other treatments in patients (i.e., DNA-interacting cytostatic drugs).[4]
- However, some TKIs are associated with significant undesirable effects and toxicities, and due to the safety profile of such TKIs, regulatory agencies have shown some resistance in performing clinical trials enrolling HVs.[5]
- The FDA and EMA (European Medicines Agency) have posted product-specific guidance's (PSGs) on their websites. They summarize the relevant study design principles and study population for demonstration of BE, namely for several TKIs, however, the requirements vary depending on the agency (**Table 1**).
- Altasciences has performed more than 50 studies with 8 TKIs in over 1700 HVs, representing an important collection of data. Forty percent (40%) of these studies have been performed with imatinib and sunitinib, 2 drugs for which the FDA suggests enrolling patients versus HVs according to EMA for BE studies.
- A retrospective evaluation of 53 crossover TKI studies has been conducted to characterize the safety and tolerability profile in HVs following a single dose administration.

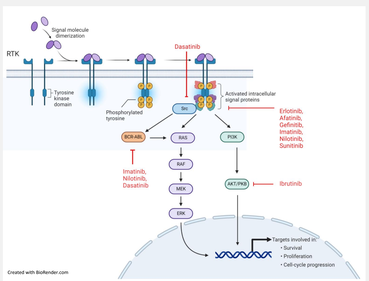


**Figure 1:** Schematic Model of the Involvement of Tyrosine Kinases in Tumorigenic Pathways and Their Inhibition by TKIs

**Table 1:** Comparison of FDA and EMA Requirements on Population and Design for Bioequivalence Studies With TKIs

| TKI | FDA | | EMA | |
|---|---|---|---|---|
| | Population | Design | Population | Design |
| Imatinib | Patients | Steady state | HVs | Single dose |
| Lapatinib | HVs | Single dose | Patients | Steady state |
| Olaparib | Patients | Steady state | Patients | Steady state |
| Pazopanib | Patients | Steady state | HVs | Single dose |
| Sunitinib | Patients | Steady state | HVs | Single dose |
| Vandetanib | Patients | Steady state | HVs | Single dose |
| Vemurafenib | Patients | Steady state | Patients | Steady state |

AKT/PKB: AKT/protein kinase B, BCR-ABL: breakpoint cluster-Abelson, ERK: extracellular signal-regulated kinase, MEK: mitogen-activated protein kinase, PI3K: phosphoinositide 3-kinase, RAF: rapidly accelerated fibrosarcoma kinase family, RAS: Rat sarcoma virus, RTK: Receptor tyrosine kinases, Src: SCR tyrosine kinase family

## METHOD

**Table 2:** General Design Information on 53 TKI Studies

| TKI | Number of studies | Conditions Fast / Fed | Number of studies based on number of periods | | |
|---|---|---|---|---|---|
| | | | 2 periods | 3 periods | 4 periods |
| Afatinib | 2 | Fast | 2 | - | - |
| Dasatinib | 10 | Fast | 3 | 1 | 2 |
| | | Fed | 1 | 1 | 2 |
| Erlotinib | 5 | Fast | 5 | - | - |
| Gefitinib | 6 | Fast | 6 | - | - |
| Ibrutinib | 5 | Fast | - | - | 3 |
| | | Fed | - | - | 2 |
| Imatinib | 18 | Fast | 4 | - | - |
| | | Fed | 11 | 3 | - |
| Nilotinib | 4 | Fast | 1 | - | 1 |
| | | Fast & Fed | - | 2 | - |
| Sunitinib | 3 | Fast | 3 | - | - |

A review of Altasciences' study database was performed to identify the clinical trials meeting the following criteria:

- Investigational product: TKI
- Design: single dose BE crossover studies (**Table 2**)
- Population (**Table 3**):
  - Healthy male or female of at least 18 years of age.
  - Negative pregnancy test for female of childbearing potential subjects.
  - Healthy according to medical history, complete physical examination (including vital signs), electrocardiogram (ECG), and laboratory tests, including serology, and negative screening of alcohol and drug abuse.
- Conditions: fasting conditions (overnight fast) or fed conditions (30 minutes after a high-fat, high-calorie meal)
- Washout: at least 5 times the elimination mean half-life
- On-study tests: Vital signs, ECG, laboratory tests, where applicable
- End-of–study: AE, laboratory tests, symptom-oriented physical examination, ECG, where applicable

## RESULTS

The majority of healthy volunteers enrolled in the studies were males, and for Imanitib studies no females were enrolled.

**Table 3:** Demographic Data

| Characteristics | | Afatinib | Dasatinib | Erlotinib | Gefitinib | Ibrutinib | Imatinib | Nilotinib | Sunitinib | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | | 2 | 10 | 5 | 6 | 5 | 18 | 4 | 3 | 53 |
| Number of subjects | | 112 | 285 | 256 | 326 | 131 | 439 | 130 | 54 | 1733 |
| Sex N (%) | Male | 79 (71) | 276 (97) | 241 (94) | 306 (94) | 100 (76) | 439 (100) | 88 (68) | 48 (89) | 1577 (91) |
| | Female | 33 (29) | 9 (3) | 15 (6) | 20 (6) | 31 (24) | - | 42 (32) | 11 (11) | 156 (9) |
| Race N (%) | White | 102 (91) | 213 (75) | 217 (85) | 279 (86) | 113 (86) | 397 (90) | 115 (88) | 54 (100) | 1490 (86) |
| | Black or African American | 5 (4) | 50 (18) | 29 (11) | 33 (10) | 8 (6) | 34 (8) | 12 (9) | - | 171 (10) |
| | Asian | 3 (3) | 13 (5) | 6 (2) | 10 (3) | 6 (5) | 4 (1) | 2 (2) | - | 44 (3) |
| | Other | 2 (2) | 9 (3) | 4 (2) | 4 (1) | 4 (3) | 4 (1) | 1 (1) | - | 28 (2) |
| BMI (kg/m²) Mean (range) | | 25.5 (19.5-30.0) | 25.9 (19.3-32.0) | 25.2 (19.2-30.0) | 25.7 (18.8-29.9) | 26.1 (19.3-30.0) | 25.2 (19.0-29.9) | 25.9 (19.1-30.0) | 25.7 (20.5-29.9) | 25.7 (18.8-32.0) |
| Age (years) Mean (range) | | 45 (18-76) | 34 (18-55) | 37 (19-65) | 38 (18-63) | 44 (18-65) | 37 (18-55) | 44 (19-64) | 45 (22-65) | 41 (18-76) |

BMI: Body Mass Index

Overall, a total of 13 subjects out of the 1733 subjects (0.75%) who were administered a TKI were discontinued from the study by the Principal Investigator for safety reasons:

- 8 subjects were withdrawn following the administration of the Test product
- 4 subjects were withdrawn following the administration of the Reference product.
- One discontinuation occurred at check-in of period 2.

**Table 4:** Percentage of Discontinued Subjects for Safety Reasons

| TKI | Number of subjects included (N) | Discontinued subjects N (%) | Description of AE | Period | Treatment | TEAE |
|---|---|---|---|---|---|---|
| Ibrutinib | 131 | 4 (3.1%) | Platelet count | 3 | Reference | Yes |
| | | | Out-of-range hematology values | 1 | Test-3 | NA |
| | | | Blood in urine | 1 | Test-3 | No |
| | | | Vomiting | 1 | Test-3 | Yes |
| Erlotinib | 256 | 3 (1.2%) | Generalized rash | 1 | Reference | Yes |
| | | | Blood in stool | 1 | Test | Yes |
| | | | Drug hypersensitivity | 1 | Test | Yes |
| Gefitinib | 326 | 3 (≤ 1%) | Out-of-range systolic/diastolic blood pressure | 2 | Check in | NA |
| | | | Ocular hyperaemia | 2 | Test | NA |
| | | | Mild abscess | 1 | Test | No |
| Imatinib | 439 | 2 (≤ 1%) | Allergic rash | 1 | Reference | Yes |
| | | | Gastroenteritis | 1 | Test | No |
| Dasatinib | 285 | 1 (≤ 1%) | Drug hypersensitivity | 2 | Reference | Yes |
| Afatinib | 112 | 0 | - | - | - | - |
| Nilotinib | 130 | 0 | - | - | - | - |
| Sunitinib | 54 | 0 | - | - | - | - |

NA: Not Available; N: number of subjects; AE: adverse event

In crossover studies with single dose administration, under 3% of subjects (ranging from 0-10% depending on the TKI) reported laboratory tests TEAEs.
All out-of-range values were repeated until resolution or judged as requiring no further follow-ups by the investigator.

**Table 5:** Number of Drug Related Treatment Emergent Adverse Events and Laboratory Test

| Characteristics | Afatinib | Dasatinib | Erlotinib | Gefitinib | Ibrutinib | Imatinib | Nilotinib | Sunitinib | Total |
|---|---|---|---|---|---|---|---|---|---|
| Blood bilirubin increased | - | - | - | - | - | 2 | - | - | 2 |
| Blood creatine phosphokinase increased | - | - | 9 | - | - | - | - | - | 9 |
| Blood creatinine increased | - | 1 | - | - | 1 | 1 | - | 4 | 4 |
| Blood potassium increased | - | - | - | - | - | 1 | - | - | 1 |
| Hepatic enzyme increased | - | - | 2 | 1 | 1 | 5 | - | - | 9 |
| Neutrophil count decreased | - | - | 1 | - | - | 4 | - | - | 5 |
| Platelet count decreased | - | - | - | - | 1 | - | - | - | 1 |
| White blood cell count increased | - | 1 | 1 | 1 | - | - | - | - | 3 |
| Number of subjects | 112 | 285 | 256 | 326 | 131 | 439 | 130 | 54 | 1733 |
| Number (%) of subjects with at least 1 laboratory tests TEAE | 0 | 2 (1%) | 13 (5%) | 2 (1%) | 3 (2%) | 13 (3%) | 0 | 4 (7%) | 34 (2%) |

A total of 1080 drug-related Treatment Emergent Adverse Events (TEAEs) were reported and involved a total of 19 System Organ Class (SOC) and 141 Medical Dictionary for Regulatory Activities (MedDRa) preferred terms, mainly including nervous system disorders (headache, somnolence, and dizziness), gastrointestinal disorders (nausea, diarrhea, vomiting, and abdominal pain), general disorders (fatigue) and skin and subcutaneous tissue disorders.

**Table 6:** System Organ Class of the Most Common Drug-Related Treatment Emergent Adverse Events

| | Afatinib | Dasatinib | Erlotinib | Gefitinib | Ibrutinib | Imatinib | Nilotinib | Sunitinib |
|---|---|---|---|---|---|---|---|---|
| NERVOUS SYSTEM DISORDERS[a] | 25 (32.5) | 213 (57.3) | 23 (21.7) | 33 (35.5) | 17 (27.0) | 108 (38.8) | 35 (55.6) | 6 (21.4) |
| Headache[b] | 14 (18.2) | 200 (53.8) | 13 (12.3) | 15 (16.1) | 6 (9.5) | 46 (16.5) | 31 (49.2) | 5 (17.9) |
| Somnolence[b] | 3 (3.9) | 6 (1.6) | 7 (6.6) | 5 (5.4) | 6 (9.5) | 50 (18.0) | 1 (1.6) | - |
| Dizziness[b] | 5 (6.5) | 6 (1.6) | 2 (1.9) | 5 (5.4) | 3 (4.8) | 7 (2.5) | 2 (3.2) | - |
| GASTROINTESTINAL DISORDERS[a] | 27 (35.1) | 75 (20.2) | 26 (24.5) | 18 (19.4) | 9 (14.3) | 71 (25.5) | 13 (20.6) | 13 (46.4) |
| Nausea[b] | 9 (11.7) | 39 (10.5) | 5 (4.7) | 3 (3.2) | 5 (7.9) | 39 (14.0) | 5 (7.9) | 4 (14.3) |
| Diarrhea[b] | 8 (10.4) | 6 (1.6) | 10 (9.4) | 5 (5.4) | 1 (1.6) | 6 (2.2) | 2 (3.2) | 1 (3.6) |
| Vomiting[b] | - | 16 (4.3) | 1 (<1.0) | 1 (1.1) | 1 (1.6) | 6 (2.2) | 2 (3.2) | - |
| Abdominal Pain[b] | 3 (3.9) | 1 (<1.0) | 4 (3.8) | 3 (3.2) | - | 5 (1.8) | 1 (1.6) | - |
| GENERAL DISORDERS[a] | 3 (3.9) | 33 (8.9) | 9 (8.5) | 14 (15.1) | 9 (14.3) | 21 (7.6) | 2 (3.2) | 2 (7.1) |
| Fatigue | 1 (1.3) | 9 (2.4) | 5 (4.7) | 9 (9.7) | 2 (3.2) | 15 (5.4) | - | 2 (7.1) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS[a] | 6 (7.8) | 13 (3.5) | 13 (12.3) | 11 (11.8) | - | 16 (5.8) | 1 (1.6) | 1 (3.6) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS[a] | 6 (7.8) | 2 (<1.0) | 5 (4.7) | 3 (3.2) | 6 (9.5) | 21 (7.6) | 2 (3.2) | 4 (14.3) |
| OTHER[a] | 10 (13.0) | 36 (9.7) | 30 (28.3) | 14 (15.1) | 22 (34.9) | 41 (14.7) | 10 (15.9) | 2 (7.1) |

N(%); [a] The sum of percentages of SOCs may not equal 100% due to rounding rules, [b] The sum of AEs per SOC may not equal to the total number of AEs, as only the main MedDRa are reported.

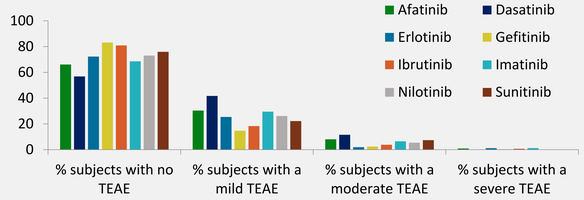


**Figure 2:** Percentage of Subjects With Drug Related Treatment Emergent Adverse Events

The evaluation of side effects presented here is reported using the Common Terminology Criteria for Adverse Events (CTCAE) scale. Only TEAEs of level 1 Mild, 2 Moderate, and 3 Severe were reported in our retrospective evaluation.

Figure 2 reports the percentage of subjects with at least one drug-related TEAE, classified by severity:

- The majority of HVs did not experience any TEAEs (ranging from 57-83% depending on the TKI administered).
- On average, ~28% of subjects reported a drug-related TEAE (ranging from 17-43% depending on the TKI administered).
  - Mild adverse events account for approximately 85% of drug-related TEAEs while moderate and severe adverse events account for approximately 12.5% and 2.5% of drug-related TEAEs, respectively.
- No life-threatening TEAEs or deaths were recorded.

## SUMMARY

The safety profile analysis of the 53 studies performed in 8 different TKIs at Altasciences reported the following:

- Approximately 72% of subjects did not report drug-related TEAEs.
- The majority of drug-related TEAEs were of mild severity (85% of cases), very few severe drug-related TEAEs were recorded (2.5%) and no life-threatening TEAEs or deaths were recorded.
- Very few subjects (≤ 3%) were discontinued from the studies by the Principal Investigator because of adverse events.
- The most commonly reported SOC of drug-related TEAEs included nervous system disorders, gastrointestinal disorders, and general disorders.
- The most commonly reported MedDRa terms of drug-related TEAEs included headache, nausea, somnolence, fatigue, and diarrhea.
- The number of periods (up to 4) did not appear to correlate with an increase in AEs (data not shown).
- Reported TEAEs were transient and reversible.
- Based on the 53 studies performed at Altasciences, these 8 TKIs are considered to be safe and well tolerated in HVs following a single dose crossover study. This experience follows the EMA recommendations but challenges certain FDA recommendations to perform multiple-dose BE studies in patients.

## CONCLUSION

Clinically, there are very few contraindications for TKIs. Considering the use of TKIs in life-extending cancer therapy, the benefits associated with TKI use outweigh the risks. The evaluation of the safety profile of 8 TKIs contributes to the existing body of literature reporting that TKIs are generally safe and well-tolerated in clinical trials conducted in HVs following single-dose administration. Such safety profile validation is important for further inclusion of HVs in oncology early phase clinical trials.

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