Short Communication

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Pregnancy outcomes in patients treated with bosutinib

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Aim: Preclinical studies have shown reproductive toxicity with bosutinib, but little is known about its effects during conception or pregnancy in humans. **Methods:** Pregnancy cases in patients receiving bosutinib were identified from the Pfizer safety database. **Results:** Thirty-three pregnancy reports were identified. Sixteen cases of maternal exposure: six live births, four abortions and six with unknown outcomes. Seventeen instances of paternal exposure: nine live births, five abortions and three with unknown outcomes. **Conclusion:** Adverse effects of bosutinib exposure at conception or during pregnancy in humans cannot be excluded, particularly if therapy is not interrupted upon recognition of pregnancy. Contraceptive use is recommended for female patients receiving bosutinib, and patients should be made aware of the potential risks associated with bosutinib use during pregnancy.

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A growing proportion of patients with chronic myeloid leukemia (CML) are of childbearing age, with approximately 20% new cases from the USA diagnosed in patients aged <45 years [1]. Coupled with improved prognosis in CML and patients reaching their normal life expectancy, fertility and pregnancy issues while on tyrosine kinase inhibitor (TKI) therapy are common concerns for patients and healthcare providers [2–4].

In preclinical and clinical studies, adverse effects on prenatal development and congenital abnormalities have been observed during treatment with imatinib, dasatinib and nilotinib [5–11]. Bosutinib is approved for the treatment of newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) CML, as well as chronic phase, accelerated phase or blast phase Ph+ CML with resistance or intolerance to prior therapy [12,13]. Reproductive toxicity and adverse developmental outcomes have also been reported in preclinical studies of bosutinib [12,13]. However, little is known about the effects of bosutinib during conception or pregnancy in humans [12,13]. The objective of this report is to describe pregnancy outcomes in bosutinib-treated patients.

Methods

Pregnancy cases reported until February 28, 2018, were identified by searching the Pfizer safety database using the standardized Medical Dictionary for Regulatory Activities query 'Pregnancy and Neonatal Topics' among patients receiving bosutinib.

The Pfizer safety database contains adverse event reports from patients, healthcare professionals, registries and licensing partners and literature reports for Pfizer's products. The database contains serious adverse event reports and pregnancy reports from investigational studies and nonresearch postmarketing studies, regardless of causality.

For each case, all available information was collected, as was any follow-up information received, and included age, sex (maternal or paternal exposure), bosutinib dose, concomitant treatments and pregnancy outcomes. As

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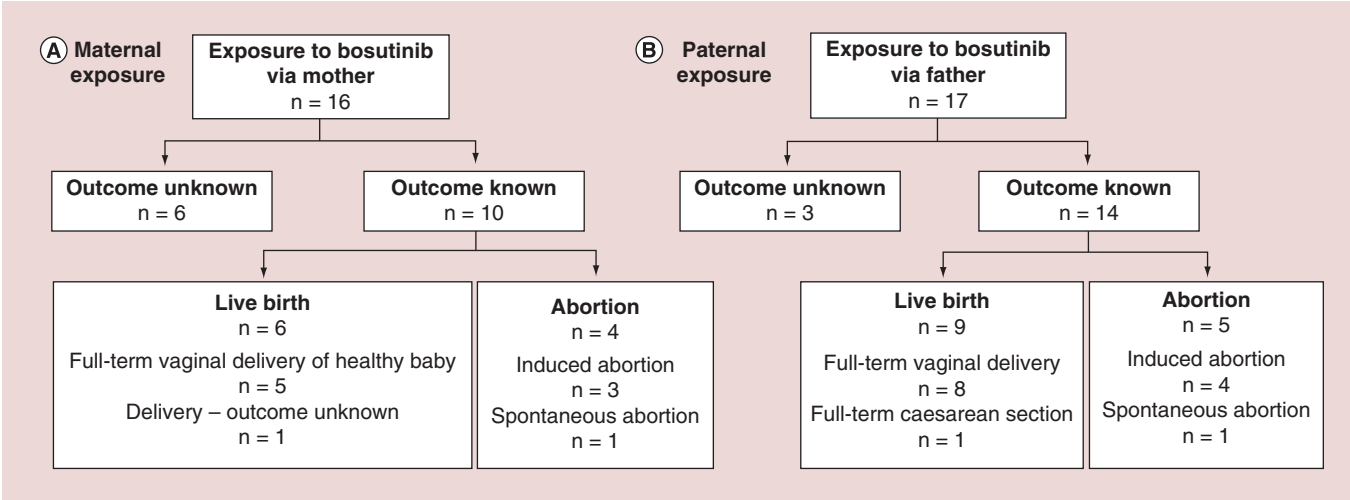

Figure 1. Pfizer safety database pregnancy cases of bosutinib exposure via **(A)** the mother and **(B)** the father.

part of routine pharmacovigilance, pregnancy reports are followed-up prospectively until the pregnancy outcome is known, using an 'Exposure During Pregnancy Follow-up Questionnaire'. The form requested details such as estimated date of conception; gestation at the time of exposure; relevant family history; exposure to relevant medical, environmental or occupational products; obstetrical history (e.g., previous pregnancies and their outcome); date of birth; pregnancy outcomes; and details on the infant (e.g., any abnormalities, sex, weight and length). Therapy duration was calculated based on the start and stop dates for treatment. The relatedness of events to bosutinib was determined by the healthcare provider.

Results

As of February 28, 2018, a total of 33 pregnancies were identified in patients receiving bosutinib, including 16 with maternal and 17 with paternal exposure (Figure 1). In 24 instances, the outcome of the pregnancy was known from the reports, of which 20 were from clinical trials; for the other nine cases, the outcome was unknown.

Maternal exposure

Of the 16 cases of maternal exposure (age range: 23–35 years), 6 resulted in live births, 4 resulted in abortions and 6 had unknown outcomes. In five of the six live births (Table 1), the mothers discontinued bosutinib (5 weeks' gestational age: n = 2; unspecified timing: n = 3); the babies were healthy at birth and born via vaginal delivery. Four of the six live births reached full term and the weight range of the babies (n = 3) was 3.0–3.5 kg. Information was unavailable for the remaining two live births.

There were three induced abortions: two were by patient choice and one was a partial molar pregnancy requiring dilation and curettage. One spontaneous abortion (gestational age unknown) was reported and was due to a suspected ectopic pregnancy in a 34-year-old patient receiving bosutinib 500-mg once daily for the treatment of CML. The ectopic pregnancy was considered by the healthcare provider to be unrelated to bosutinib (Table 2).

The six pregnancies with unknown outcomes included two females (aged 29 and 28 years of age) who received bosutinib for the treatment of CML; one each from a clinical trial and nonclinical study program, respectively. The remaining four cases were spontaneously reported by a nurse via a Pfizer sales representative and contained limited information; however, bosutinib was reported as discontinued (date unspecified) for all four patients.

Paternal exposure

There were 17 cases of paternal exposure (age range: 26–44 years): 9 live births, 5 abortions and 3 with unknown outcomes. Known therapy duration at pregnancy confirmation was 2–75 months. Eight of the nine live births reached full term, and the pregnancy duration was unavailable for the remaining case. One baby was delivered by cesarean section. All babies were healthy at birth (Table 1).

There were four induced abortions: one was elective due to an unintended pregnancy, two were due to unknown reasons and, in the last case, it was reported that the fetus was not growing properly and the pregnancy was

Table 1. Pregnancy cases of bosutinib exposure: live births.

Setting	Age (years)	Starting bosutinib dose (mg/day)	Indication	Therapy duration† (months)	Action taken	Concomitant medications	Pregnancy duration	Delivery and outcome	Weight (kg)/height (cm) at birth
Exposure via the mother									
Clinical trial	32	600‡	1st-line CML	~23	Bosutinib permanently discontinued – first trimester, ~5 weeks gestational age	–	Full term	Vaginal healthy baby	3.5/53.0
Clinical trial	33	500	≥2nd-line CML	~76	Bosutinib permanently discontinued – first trimester, ~5 weeks gestational age	–	Full term	Vaginal healthy baby	3.0/–
Clinical trial	27	500	1st-line CML	~56§	Bosutinib discontinued (duration unknown)	SC IFN-α 4.5 million IU/d for leukocytosis and oral hydroxycarbamide 500 mg b.i.d. for leukocytosis	Full term	Vaginal healthy baby	3.3/50.0
Retrospective observational study	25	100	≥2nd-line CML	~7	Bosutinib temporarily discontinued (duration unknown) – timing unspecified	Ondansetron, tramadol and paracetamol	Full term	Vaginal healthy baby	–/–
Spontaneous report from a contactable consumer (mother) received via the program Pfizer RXPathways	–	–	–	–	Bosutinib discontinued (duration unknown) – timing unspecified	–	–	–	–/–
Clinical trial	35	500	≥2nd-line Ph+ leukemia	~1	Bosutinib permanently discontinued – timing unspecified	Prochlorperazine maleate and esomeprazole	–	Vaginal healthy baby	–/–
Exposure via the father									
Clinical trial	39	500	≥2nd-line Ph+ leukemia	~10	Bosutinib continued unchanged	–	Full term	Vaginal healthy baby	3.8/50.0
Clinical trial	40	500	≥2nd-line Ph+ leukemia	~42	Bosutinib continued unchanged	–	Full term	Vaginal healthy baby	4.0/53.0

† At pregnancy confirmation.
‡ Known dose at time of event.
§ Patient was noncompliant while using study drug and discontinued prior to pregnancy confirmation.
¶ At estimated date of conception.
b.i.d.: Twice daily; CML: Chronic myeloid leukemia; IFN: Interferon; Ph+: Philadelphia chromosome-positive; q.d.: Daily.

Table 1. Pregnancy cases of bosutinib exposure: live births (cont.).

Setting	Age (years)	Starting bosutinib dose (mg/day)	Indication	Therapy duration† (months)	Action taken	Concomitant medications	Pregnancy duration	Delivery and outcome	Weight (kg)/height (cm) at birth
Clinical trial	44	500	≥1st-line CML	~66	Bosutinib continued unchanged	Mecobalamin 500-μg weekly injection, herbal extracts, oral fursultiamine, neurotropin injection q.d., oral loxoprofen sodium for cerebral palsyOral mecobalamin for radial nerve palsy Betamethasone, betamethasone topical ointment, neomycin sulfate topical ointment, chlorphenamine maleate and olopatadine hydrochloride ophthalmic eye drops at 0.1% for atopic dermatitis Tranilast ophthalmic eye drops at 0.5% and fluorometholone ophthalmic eye drops at 0.1% for atopic conjunctivitis Sodium picosulfate liquid, and *Bacillus subtilis*, *Lactobacillus acidophilus*, *Streptococcus faecalis* oral powder at 1 g, 3x/d for constipation	Full term	Vaginal healthy baby	–/–
Clinical trial	30	400	1st-line CML	~19	Bosutinib continued at 600 mg/d	–	Full term	Cesarian section healthy baby	3.5/55.0
Spontaneous report from a contactable physician via the program Pfizer.com Contact Us Clinical Research	–	500	CML	–	–	–	–	Vaginal healthy baby	–/–
Clinical trial	44	500	≥1st-line CML	~75	Bosutinib continued unchanged	Gelarferro powder, at 1 dosage form q.d. to prevent low iron	Full term	Vaginal healthy baby	3.2/–
Clinical trial	42	400	1st-line CML	~21	Bosutinib continued at 300 mg/d	Simvastatin, enalapril maleate, bisoprolol fumarate, acetaminophen, loperamide hydrochloride and granisetron	Full term	Vaginal healthy baby	2.8/46.0
Clinical trial	31	400	1st-line CML	~24	Bosutinib continued unchanged	Ergocalciferol/retinol 1 dosage form q.d., amoxicillin 1 g bid, paracetamol 1000 mg as needed, naphazoline 1 dosage form as needed, clotrimazole 1 dosage form q.d., lidocaine hydrochloride/nifedipine 1 dosage form q.d.	Full term	Vaginal healthy baby	–/–
Clinical trial	–	500	1st-line CML	~2¶	Bosutinib continued unchanged	–	Full term	Vaginal healthy baby	–/–

† At pregnancy confirmation.
‡ Known dose at time of event.
§ Patient was noncompliant while using study drug and discontinued prior to pregnancy confirmation.
¶ At estimated date of conception.
b.i.d.: Twice daily; CML: Chronic myeloid leukemia; IFN: Interferon; Ph+: Philadelphia chromosome-positive; q.d.: Daily.

Table 2. Pregnancy cases of bosutinib exposure: abortions.

Setting	Age (years)	Starting bosutinib dose (mg/day)	Indication	Therapy duration† (months)	Action taken	Relationship to bosutinib exposure	Details
Exposure via the mother							
Spontaneous report from a contactable physician received via a sales representative	–	300	–	–	–	A drug-event causal association cannot be ruled out	The patient became pregnant while on bosutinib for an unspecified condition. The patient's pregnancy was aborted on an unspecified date at the patient's request
Clinical trial	35	400	1st-line CML	~24	Bosutinib permanently discontinued after elective abortion	Unrelated	The patient became pregnant while receiving bosutinib. The patient chose to have an elective abortion at week 5 due to her personal decision not to have more children Concomitant medication included oral bendroflumethiazide 2.5 mg q.d. and oral enalapril 10 mg q.d. for hypertension, oral loperamide hydrochloride 2 mg prn, oral clemastine fumarate 1 mg prn and oral desloratadine 5 mg prn
Clinical trial	34	500	1st-line CML	<1‡	Dose not changed	Unrelated	The patient was thought to have become pregnant prior to enrolling in the study. Upon examination on a date after the patient began bosutinib therapy, the patient's physician reported a suspected spontaneous abortion of an ectopic pregnancy
Clinical trial	23	400	1st-line CML	~23	Bosutinib permanently discontinued ~7 weeks' gestational age	Unrelated	The patient became pregnant while receiving bosutinib. The outcome of the pregnancy was partial molar pregnancy requiring dilation and curettage Concomitant medication included diphenhydramine hydrochloride, acetylsalicylic acid, caffeine, paracetamol, salicylamide, ondansetron, sumatriptan and ferrous sulfate
Exposure via the father							
Clinical trial	–	500	≥2nd-line CML	–	Bosutinib continued unchanged	Unrelated	The patient began taking bosutinib for CML in February 2009. On an unknown date in 2009, a pregnancy of the patient's partner was confirmed. On June 20, 2009, an elective abortion was carried out
Clinical trial	35	500	≥2nd-line CML	~22§	Bosutinib continued unchanged	Unrelated	The patient's partner became pregnant ~22 months after the patient began therapy. On December 18, 2009, the partner underwent a medical abortion of the pregnancy
Clinical trial	32	500	≥2nd-line leukemia (unspecified)	~5	Bosutinib continued unchanged	Unrelated	The patient began taking bosutinib in August 2007. In January 2008, a pregnancy of the patient's partner was confirmed. The partner experienced a spontaneous abortion in May 2008. Fetal biopsy revealed basal deciduitis with necrosis foci and bleeding

† From start of treatment to discontinuation of bosutinib/pregnancy confirmation.
‡ At diagnosis of ectopic pregnancy.
§ At estimated date of conception.
CML: Chronic myeloid leukemia; prn: As needed; q.d.: Daily.

Table 2. Pregnancy cases of bosutinib exposure: abortions (cont.).

Setting	Age (years)	Starting bosutinib dose (mg/day)	Indication	Therapy duration† (months)	Action taken	Relationship to bosutinib exposure	Details
Clinical trial	39	400	1st-line CML	~7	Bosutinib continued unchanged	Unrelated	The patient began taking bosutinib in April 2015 for CML. An unintended pregnancy of the patient's partner was confirmed in December 2015. Three weeks later, the partner underwent an elective termination via curettage induced abortion Concomitant medication was prednicarbate
Clinical trial	26	400	1st-line CML	~7	–	Unrelated	The patient began taking bosutinib for CML in August 2015. In February 2016, a pregnancy of the patient's partner with a gestational age of 8 weeks was confirmed. A week later, the partner communicated to the patient that the fetus was not growing and an abortion of the pregnancy would be performed. No congenital abnormality was confirmed No concomitant medication

† From start of treatment to discontinuation of bosutinib/pregnancy confirmation.
‡ At diagnosis of ectopic pregnancy.
§ At estimated date of conception.
CML: Chronic myeloid leukemia; prn: As needed; q.d.: Daily.

subsequently terminated (there was no confirmation of congenital abnormality and further information was not available). One case of spontaneous abortion was reported and considered by the healthcare provider to be unrelated to bosutinib, fetal biopsy revealed basal deciduitis with necrosis foci and bleeding (Table 2).

One of the three pregnancy cases with unknown outcomes involved a 31-year-old male who was receiving bosutinib 400-mg once daily for the treatment of CML in a clinical trial. The remaining two cases involved a 33-year-old male receiving bosutinib for CML, and who fathered two children (by two women at the same time) whilst on treatment; these cases were a spontaneous report from a non-contactable physician received via a Pfizer sales representative.

Discussion

Despite limited available data, this report presents the most extensive information to date on pregnancy among bosutinib-treated patients. Nearly half of the pregnancies resulted in healthy newborns, with the next most common outcome being abortion, most frequently induced. None of the abortion cases were considered by the healthcare provider to be related to bosutinib. Acknowledging the small sample size, the incidence of spontaneous abortion in this database does not appear to be higher than that reported in the general population [14–17]. Furthermore, no specific bosutinib-induced abnormalities were identified in this series, including no instances of the congenital abnormalities observed in animal models exposed to TKIs [5–13].

Reports have recommended a collaborative approach between the patient and the hematology and obstetric teams regarding the management of pregnancy during TKI treatment for CML. Ideally, female patients with CML who wish to become pregnant should do so when in sustained molecular response and should stop therapy upon conception [7,9,10,18,19]. The effects of bosutinib on pregnancy experienced in the current study were largely similar to those reported for other TKIs, and female patients with CML should not be exposed to TKIs during pregnancy [5–11,20–23]. There was no evidence of adverse effects on conception and delivery for female partners of male patients with CML being treated with TKIs [5–11,20–22].

One important aspect is the amount of unavailable data in this and other similar reports. Since nearly all clinical trials exclude pregnant patients, prospective data generation is nearly impossible. Better mechanisms need to be developed to collect this information for this and other cancer therapies. These should include a more definitive commitment and responsibility from physicians to report such instances, perhaps with the development of a standardized format that is used worldwide, and some oversight, enforcement and assistance from regulatory authorities to ensure that such gaps are closed.

In line with European Leukemia Net and National Comprehensive Cancer Network guidelines, discussions regarding the impact of CML and treatment with bosutinib (and other TKIs) on fertility and pregnancy should be in collaboration with an obstetrician [12,13,24,25]. The current prescribing information for bosutinib advises on the potential for fetal harm during treatment; bosutinib is therefore not recommended for use at any time during pregnancy [12,13]. European Leukemia Net and National Comprehensive Cancer Network guidelines also advise that TKI treatment be discontinued in the event of pregnancy [24,25]. Also, based on preclinical investigations, there

Executive summary

- Preclinical studies have shown reproductive toxicity with bosutinib, but little is known about its effects during conception or pregnancy in humans.
- Following a review of a Pfizer safety database, a total of 33 pregnancies were identified in patients receiving bosutinib.
- There were 16 cases of maternal exposure: 6 live births, 4 abortions and 6 with unknown outcomes.
- There were 17 cases of paternal exposure (age range: 26–44 years): 9 live births, 5 abortions and 3 with unknown outcomes.
- Nearly half of the pregnancies resulted in healthy newborns, with the next most common outcome being abortion, most frequently induced. None of the abortion cases were considered by the healthcare provider to be related to bosutinib.
- Adverse effects of bosutinib exposure at conception or during pregnancy in humans cannot be excluded, particularly if therapy is not interrupted upon recognition of pregnancy.
- Female patients should take a pregnancy test prior to starting bosutinib treatment, and use of effective contraception during treatment is mandatory for ≥1 month after taking the last dose.
- Patients should also be made aware of the potential risks associated with bosutinib use during pregnancy.

is a risk of decreased fertility with bosutinib [12,13]. Female patients should take a pregnancy test prior to starting bosutinib treatment, and the use of effective contraception during treatment is mandatory for ≥1 month after taking the last dose. Patients should also be made aware of the potential risks associated with bosutinib use during pregnancy [12,13].

Supplementary data

A plain language summary accompanies this paper. To download the plain language summary, please visit the journal website at: https://www.futuremedicine.com/doi/10.2217/ijh-2020-0004

Author contributions

All authors were involved in the trial conception/design, and in the acquisition, analysis and interpretation of data. All authors contributed to the drafting of the manuscript and approved the final version.

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Ethical conduct of research

Not applicable – information was obtained from a Pfizer safety database. All relevant ethical approvals were obtained during the specific trials included in the safety database.

Data sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices for indications that have been approved in the USA and/or EU or in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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