FEATURED ARTICLES

Long-term safety and efficacy of imatinib in pulmonary arterial hypertension

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BACKGROUND: Imatinib is an oral inhibitor of several protein kinases implicated in the pathophysiology of pulmonary hypertension. Treatment with imatinib resulted in improved hemodynamics and exercise capacity in a controlled trial (Imatinib [QTI571] in Pulmonary Arterial Hypertension, a Randomized Efficacy Study [IMPRES]), among pulmonary arterial hypertension (PAH) patients inadequately responsive to 2 to 3 PAH-specific therapies.
METHODS: The long-term (up to 204 weeks) safety and efficacy of imatinib in this open-label extension study were reviewed until early study termination on April 16, 2014. Of 202 IMPRES-enrolled patients, 66 imatinib and 78 placebo recipients entered the extension.

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RESULTS: Overall, 93.8% (135 of 144) of patients discontinued the extension study; administrative issues (i.e., sponsor termination; 32.6%) and adverse events (31.3%) were the primary reasons for discontinuation. Nine patients completed the extension study before it was terminated. Serious and unexpected adverse events were frequent. These included 6 subdural hematomas in the extension study and 17 deaths during or within 30 days of study end. Although the patients who tolerated imatinib and remained in the extension for a longer duration did experience an improvement in functional class and walk distance, most discontinued the drug and the study.

CONCLUSIONS: Severe adverse events, significant side effects, and a high discontinuation rate limit the utility of imatinib in the treatment of PAH. These risks outweigh any possible improvements in hemodynamics and walk distance seen in those patients able to remain on drug. The off-label use of this compound in PAH is discouraged.

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Pulmonary arterial hypertension (PAH) is characterized by vascular proliferation and remodelling of small pulmonary arteries resulting in increased pulmonary vascular resistance (PVR) and right heart failure.[1] Current treatment options (prostacyclin analogs, endothelin receptor antagonists (ERA), phosphodiesterase type 5 (PDE-5) inhibitors, and guanylate cyclase (GC) stimulators) improve exercise capacity, hemodynamic variables, symptoms, and World Health Organization (WHO) functional class (FC) and decrease morbidity, defined as clinical worsening and hospitalizations.[2–15] Despite such treatments, the prognosis for patients with PAH remains poor, with survival rates variously reported as 83% to 85% at 1 year and 58% to 67% at 3 years after diagnosis.[16,17] There is a clear need for new treatments to target the underlying pathophysiology of PAH.

The earliest understanding of PAH was derived from models of vasoconstriction; early therapies targeting vasodilation showed utility in a small percentage of patients.[18] Although perturbation of the normally occurring vasoconstriction and vasodilation may remain part of the pathophysiology of PAH, it is clear from the pathology of PAH that the major abnormality is abnormal cellular proliferation resulting in progressive obliteration of the pulmonary vasculature.[1] Platelet-derived growth factor and c-KIT signaling have been shown to be important in vascular smooth muscle cell proliferation and hyperplasia in PAH[19–23] and provide potential targets for new treatments.

The Phase III Imatinib (QTI571) in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) was initiated after encouraging results with imatinib (Novartis Pharma AG, Basel, Switzerland) in patients with PAH in several case reports[24–26] and evidence of improvement in hemodynamics in a randomized, double-blind, placebo-controlled Phase II study.[27] In IMPRES, a randomized controlled trial (RCT) of imatinib vs placebo, imatinib improved exercise capacity and hemodynamics in patients with advanced PAH who had remained symptomatic on at least 2 of the currently available drug classes.[28] Patients who completed the core 24-week IMPRES study were eligible for enrollment in an open-label extension study. Here, we report safety and efficacy data as of study termination on April 16, 2014.

Methods

Study design, patients, and treatment

This is a long-term extension to the core 24-week IMPRES study, the design of which has been reported previously.[28] Patients enrolled in the core study were at least 18 years old and had symptomatic PAH with a diagnosis of Group 1 pulmonary hypertension: idiopathic or heritable PAH, PAH associated with connective tissue disease, PAH ≥ 1 year post-repair of congenital systemic-to-pulmonary shunt, or PAH associated with anorexigens or other drugs.[29] Patients were required to be receiving at least 2 PAH therapies (ERA, PDE-5 inhibitors, or prostacyclin analogs for ≥3 months) with a PVR ≥ 800 dynes · sec · cm^{-5} at screening.[28]

In the core IMPRES study, patients were randomized (1:1) to imatinib or placebo at an intended starting dose of 200 mg once daily, with subsequent up-titration to 400 mg once daily if tolerated. On completion of the 24-week core study, patients were eligible to enter the extension. Although all patients in the extension study received imatinib, treatment was dispensed in a manner that preserved blinding to the core treatment assignment until core study database lock. After the core study database lock (June 24, 2011), patients were switched to open-label drug supply. Patients who had received imatinib 200 or 400 mg remained on the same dose during the extension. Ex-placebo patients initiated imatinib 200 mg once daily on entering the extension, with up-titration to 400 mg after 2 weeks. Dose titration between 200 and 400 mg was allowed based on tolerability.

The study was designed, implemented, and reported in accordance with the International Conference on Harmonisation "Harmonised Tripartite Guidelines for Good Clinical Practice" and all applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. All patients gave written, informed consent to participate in the study. The study was terminated on April 16, 2014, and results up to this date are presented here.

The primary objective of the IMPRES extension was to evaluate the long-term safety and tolerability of imatinib. Secondary objectives included evaluation of the long-term efficacy of imatinib expressed as change in 6-minute walk distance (6MWD) from core study baseline, WHO FC, and assessment of time to clinical worsening (TTCW) events.

Safety assessments

Safety assessments consisted of recording all adverse events (AEs) and serious AEs (SAEs). All AEs starting after the first dose of

medication in the extension study were analyzed up to the date of the last study treatment plus 7 days (30 days for SAEs) or the data cutoff date, whichever was earlier. Hematology, blood chemistry, edema, N-terminal prohormone brain natriuretic peptide, urine analysis, vital signs, echocardiograms, and electrocardiograms were also recorded. An external data monitoring committee monitored safety during the study. Overnight hospitalizations and any patient deaths recorded during the study or within 30 days of study drug discontinuation were independently adjudicated.

Efficacy assessments

Six-minute walk tests (6MWTs) were performed according to American Thoracic Society guidelines[30] at Weeks 12, 24, 48, 72, 96, 120, 144, 156, and 204 of the extension. 6MWTs were also conducted at Week 0 of the extension if none had been performed within the past 4 weeks.

The functional status of patients was assessed over the course of the study according to the WHO FC. The TTCW assessment included time to all-cause mortality, overnight hospitalization for worsening PAH, worsening of WHO FC by $\geq$ 1 level and a 15% decrease in the 6MWD vs baseline. This was confirmed by 2 6MWTs at 2 consecutive visits. The time of the first 15% decrease was the TTCW once it was confirmed at the following visit.

Statistical analyses

Here, we report safety and efficacy data as of study termination on April 16, 2014. For assessments performed at study visits (i.e., 6MWT, WHO FC, hematology, blood chemistry, edema, N-terminal prohormone brain natriuretic peptide, urine analysis, vital signs, echocardiograms, electrocardiograms) all patient data collected up to

the last study visit before the data cutoff date were included. For data not based on the last study visit (i.e., TTCW, AEs, and exposure), all data up to the date of study completion/withdrawal or data cutoff date, whichever was earlier, were analyzed.

Patients who were randomized into the core study and took at least one dose of extension study medication before the data cut-off date were included in the analysis. Patients were analyzed according to the treatment to which they were randomized in the core study.

Most of the analyses in this open-label extension are based on summary statistics (i.e., mean, standard deviation, median, range, and patient counts). The exception to this is TTCW, which has been summarized using the Kaplan-Meier method. In this analysis, all data from the core and extension study are combined. Patients with no clinical worsening were censored at the study completion visit of the extension study, study withdrawal (core or extension) plus 30 days, or data cutoff date, whichever occurred first.

Results

Disposition and baseline characteristics

The core study randomized 103 patients to imatinib and 99 to placebo (Figure 1). The core study was completed by 69 imatinib recipients and 81 placebo recipients, 66 and 78 patients, respectively entered the extension, representing an unusually high dropout rate for most PAH studies. Overall, 93.8% (135 of 144) of patients discontinued the extension study. Early termination of the extension study on April 16, 2014, was the most common reason for discontinuation (32.6%; 47 patients were ongoing at sponsor termination of study). AEs were the next most common reason for discontinuation (31.3%). Nine patients (all from Germany)
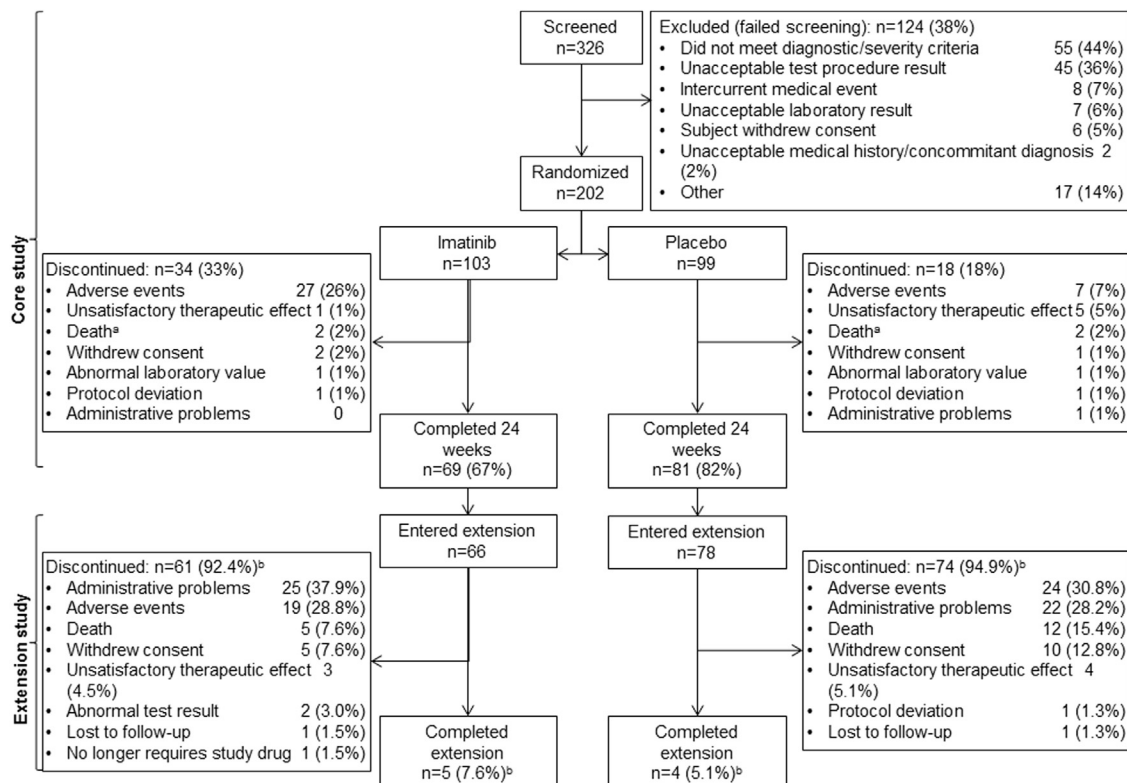
Figure 1   Patient disposition. [a]Two additional deaths occurred, 1 in each group, within 30 days of study drug discontinuation. [b]Percentages are expressed as the percentage of patients entering the extension. Patients could be excluded (fail screening) for more than 1 reason.

completed the extension study before its termination to Year 3, and these sites did not proceed with the amendment, which would have continued their patients to Year 4.

Baseline demographic and clinical characteristics were well balanced between treatment groups in the core study and extension (Table 1). Characteristics were also similar between the participants in the core study and those taking part in the extension.

Safety and tolerability

At the time of study termination, mean exposure to imatinib, including the core and extension periods, was 931 days in the ex-imatinib group, and 590 days in the ex-placebo group.

A total of 35 deaths have been reported since initiation of the core IMPRES study, which includes 8 deaths that occurred more than 30 days after a patient stopped study participation. All of these deaths were reviewed and adjudicated. As has been previously reported, 6 deaths occurred during the core study (3 in both the imatinib and placebo groups) and an additional 4 deaths (2 in both the ex-imatinib and ex-placebo groups) occurred after core study completion in patients who did not participate in the extension study. Of the 144 patients enrolled in the extension study, 17 died during the study or within 30 days after study participation: 12 in the core placebo group (9 while on treatment and 3 within 30 days of study completion) and 5 in the ex-imatinib group (3 while on

Table 1 Demographic and Clinical Characteristics of the Study Population[a]

Variables[b]	Core study		Extension study	
	Imatinib (n = 103)	Placebo (n = 98)	Ex-imatinib (n = 66)	Ex-placebo (n = 78)
Age, years	50 (18–77)	48 (18–77)	48.5 (18–77)	45.5 (18–77)
Age distribution				
18–39 years	28 (27)	35 (36)	20 (30)	28 (36)
40–64 years	57 (55)	54 (55)	33 (50)	44 (56)
≥65 years	18 (18)	9 (9)	13 (20)	6 (8)
Sex				
Male	20 (19)	19 (19)	9 (14)	15 (19)
Female	83 (81)	79 (81)	57 (86)	63 (81)
Race				
Caucasian	77 (75)	72 (74)	53 (80)	54 (69)
Black	4 (4)	5 (5)	3 (5)	5 (6)
Asian	19 (18)	20 (20)	9 (14)	18 (23)
Other	3 (3)	1 (1)	1 (2)	1 (1)
PAH duration, years	3.7 (0.3–41)	5.1 (0–17)	3.4 (0.3–15)	4.3 (0–17)
Type of PAH				
Idiopathic or heritable	77 (75)	74 (76)	52 (79)	60 (77)
Associated with other conditions	26 (25)	23 (23)	14 (21)	17 (22)
Other	0	1 (1)	0	1 (1)
WHO functional class				
I	1 (1)	0	1 (1.5)	0
II	23 (22)	28 (29)	15 (23)	26 (33)
III	71 (69)	65 (66)	47 (71)	49 (63)
IV	8 (8)	5 (5)	3 (5)	3 (4)
PAH-specific background therapy				
ERA and PDE5i	32 (31)	27 (28)	19 (29)	22 (28)
ERA and PG	15 (15)	10 (10)	10 (15)	8 (10)
PG and PDE5i	14 (14)	20 (20)	9 (14)	15 (19)
ERA, PDE5i, and PG	42 (41)	41 (42)	28 (42)	33 (42)
Anti-coagulant therapy[c]				
Warfarin	31 (30)	40 (41)	23 (35)	35 (45)
Other oral anti-coagulants[d]	30 (29)	27 (28)	22 (33)	22 (28)
Sub-cutaneous anti-coagulants[e]	3 (3)	2 (2)	13 (20)	10 (13)
Intravenous heparin	0 (0)	0 (0)	2 (3)	4 (5)
6MWD, m	355 (154–450)	366 (153–446)	355 (174–450)	375 (153–446)

6MWD, 6-minute walk distance; ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type-5 inhibitors; PG, prostacyclin analogs; WHO, World Health Organization.
[a]Data for PAH-specific background therapy are from the baseline visit of the extension study, and all other data are from baseline of the core study.
[b]Continuous data are shown as mean (range) and dichotomous data as number (%).
[c]Data for the core study reflect anti-coagulant use at start of the study, and the data for the extension study reflect use at the start and during the study; anti-coagulant categories are not mutually exclusive.
[d]Includes phenprocoumon, acenocoumarol, and rivaroxaban.
[e]Includes enoxaparin, heparin, and fondaparinux.

treatment and 2 within 30 days of study completion). These 17 deaths were adjudicated, with 7 considered to be due to worsening of PAH (Supplementary Table S1, available on the jhltonline.org Web site). Supplementary Table S1 reflects deaths, time of death relative to study participation, imatinib treatment duration, and adjudicated cause of death. An additional 8 deaths are included for completeness although they occurred more than 30 days after the patient stopped study participation.

Subdural hematomas (SDHs), rarely if ever reported in prior PAH studies, occurred in 8 patients throughout the core and extension study. All patients who experienced a SDH were receiving anti-coagulation. However, the use of anti-coagulation was no more frequent in the IMPRES RCT and open-label study than has been reported in prior studies in PAH. SDH occurred in 6 patients during the extension study; 4 of the 6 patients had other contributing factors (Supplementary Table S2, available on the jhltonline.org Web site). However, other than being generally sicker, with higher PVR and routine use of 2 or 3 PAH-specific therapies, these patients were not different from those reported in other short-term and long-term PAH trials. The duration of imatinib exposure before the development of SDH ranged from 29 to 531 days, and 5 of the 8 SDHs occurred in the first 100 days of imatinib exposure (Supplementary Table S2, available on the jhltonline.org Web site). The demographics (sex, mean age, background pulmonary hypertension–specific therapies, and FC) were the same as those reported for the total IMPRES study at time of enrollment (Table 2). The mechanism of SDH remains unclear and concerning.

During the extension, 19 patients (28.8%) in the ex-imatinib group and 26 (33.3%) in the ex-placebo group discontinued due to AEs. A slightly higher proportion of patients in the ex-placebo group (97.4%) experienced AEs during the extension study compared with the ex-imatinib patients (Table 3). The most frequent AEs were nausea, peripheral edema, diarrhea, nasopharyngitis, cough, and vomiting. SAEs occurred in 67.9% of patients in the ex-placebo group and in 60.6% of patients in the ex-imatinib group (Table 3).

QTc prolongation was collected as a potential AE as proscribed by the study and was defined as > 450 msec in men and > 470 msec in women. Eighteen of 24 male patients (75%) and 29% of female patients (35/120 patients) had at least one event during this open label study that met this definition of QTc prolongation. For reference, in the core IMPRES study, 68% of male placebo patients and 22% of female placebo patients also had at least 1 event that met this definition.

We attempted to assess potentially clinically significant consequences of QTc prolongation by correlating the occurrence of syncope and death with QTc prolongation. Nine patients in the OLE had a SAE of syncope; of these, 3 (33%) had at least 1 event that met this definition of QTc prolongation. None of these patients with syncope had QTc prolongation of > 500 msec. Of the 17 deaths reported in the extension (including those within 30 days after discontinuation of drug), 4 patients (24%) had at least 1 elevated QTc interval at some point before death compared with an incidence of 30% (38 of 127) in patients who did not die.

Table 2 Demographic and Clinical Characteristics of Patients Reporting Subdural Hematoma Compared with the Overall Study Population

SDH patients vs all IMPRES	Age SDH and IMPRES all (median years)	M/F (% F)	PAH-specific background therapy[a]	WHO FC at time of first imatinib exposure	Imatinib exposure at time of SDH[b] (days)
N = 8	46[c]	F	SIL/SITAX	III	15
	47[c]	F	EPO/AMBRI	III	100
	50	F	SIL/EPO	II	67
	57	F	SIL/AMBRI	III	29
	66	F	SIL/BOS/EPO	III	218
	59	F	ILO/SIL/AMBRI	III	74
	47	M	SIL/BOS	II	531
	55	M	SIL/BOS	III	376
	52.5	2M/6F (75% F)	ERA+PDE5 3 (37.5%) ERA+PG 1 (12.5%) PG+PDE5i 1 (12.5%) All 3 3 (37.5%)	II (25%) III (75%)	N/A
IMPRES (all) N = 201	48–50	(80% F)	ERA+PDE5i 28%–31% ERA+PG 10%–15% PG+PDE5i 14%–20% All 3 41%–42%	I–II (23%–29%) III (66%–69%) IV (4%–8%)	N/A

AMBRI, ambrisentan; BOS, bosentan; EPO, epoprostenol; ERA, endothelin receptor antagonists; F, female; FC, functional class; ILO, inhaled iloprost; M, male; N/A not applicable; PDE5i, phosphodiesterase type 5 inhibitors; PG, prostacyclin analogs; SDH, subdural hematoma; SIL, sildenafil; SITAX, sitaxsentan; WHO, World Health Organization.
[a]Data for pulmonary arterial hypertension-specific background therapy is from the baseline visit of the respective study.
[b]For core imatinib patients—from Day 1 of the core study, for core placebo patients—from Day 1 of the extension study.
[c]SDH during the core study.

Table 3 Frequency of Adverse Events[a] and Serious Adverse Events[b] in Either Treatment Group

Events	Ex-imatinib (n = 66) No. (%)	Ex-placebo (n = 78) No. (%)
Adverse events	62 (93.9)	76 (97.4)
Nausea	22 (33.3)	39 (50.0)
Peripheral edema	22 (33.3)	32 (41.0)
Diarrhea	18 (27.3)	27 (34.6)
Nasopharyngitis	17 (25.8)	24 (30.8)
Cough	16 (24.2)	11 (14.1)
Vomiting	15 (22.7)	26 (33.3)
Dyspnea	13 (19.7)	8 (10.3)
Headache	12 (18.2)	24 (30.8)
Periorbital edema	12 (18.2)	24 (30.8)
Pyrexia	10 (15.2)	8 (10.3)
Fatigue	9 (13.6)	11 (14.1)
Dizziness	9 (13.6)	5 (6.4)
Muscle spasms	8 (12.1)	12 (15.4)
Pulmonary arterial hypertension	8 (12.1)	9 (11.5)
Anemia	8 (12.1)	9 (11.5)
Oropharyngeal pain	8 (12.1)	1 (1.3)
Rash	7 (10.6)	13 (16.7)
Upper respiratory tract infection	7 (10.6)	12 (15.4)
Hypotension	7 (10.6)	3 (3.8)
Right ventricular failure	6 (9.1)	8 (10.3)
Thrombocytopenia	6 (9.1)	8 (10.3)
Arthralgia	5 (7.6)	12 (15.4)
Hypokalemia	5 (7.6)	11 (14.1)
Urinary tract infection	3 (4.5)	9 (11.5)
Leukopenia	1 (1.5)	11 (14.1)
Bronchitis	1 (1.5)	8 (10.3)
Serious adverse events	40 (60.6)	53 (67.9)
Pulmonary arterial hypertension	6 (9.1)	8 (10.3)
Right ventricular failure	5 (7.6)	8 (10.3)
Device related infection	5 (7.6)	3 (3.8)
Dyspnea	4 (6.1)	5 (6.4)
Pneumonia	3 (4.5)	3 (3.8)
Respiratory failure	3 (4.5)	2 (2.6)
Anemia	3 (4.5)	2 (2.6)
Hemoptysis	3 (4.5)	1 (1.3)
Syncope	2 (3.0)	7 (9.0)
Acute renal failure	2 (3.0)	2 (2.6)
Vomiting	2 (3.0)	2 (2.6)
Hypotension	2 (3.0)	1 (1.3)
Coagulopathy	2 (3.0)	0
Diarrhea	2 (3.0)	0
Dehydration	1 (1.5)	3 (3.8)
Pyrexia	1 (1.5)	3 (3.8)
Nausea	1 (1.5)	3 (3.8)
Subdural hematoma	1 (1.5)	3 (3.8)
Leukopenia	0	3 (3.8)

[a]Totals and a breakdown of adverse events occurring in >10% patients in either group.
[b]Totals and a breakdown of serious adverse events occurring in ≥3 patients in either group.

Imatinib and tyrosine kinase inhibitors have been associated with myocardial dysfunction. Routine echocardiographic assessments did not show any evidence of left ventricular cardiac dysfunction associated with imatinib. No relevant mean changes in left ventricular ejection fraction occurred in either treatment group between core baseline and the termination of the extension (Supplementary Table S3, available on the jhltonline.org Web site).

Efficacy

Efficacy data are reported for all patients completing Weeks 12, 24, 48, 72, 96, 120, 144, and 156 of the extension study (i.e., up to 180 weeks from core study baseline). The number of patients who had completed more than 156 weeks in the extension by study termination was too small to consider for analysis. A preplanned efficacy analysis undertaken at Week 72 of the extension study (i.e., up to 96 weeks from core study baseline) showed that the improvements in 6MWD among the ex-imatinib patients seen during the core study[28] were sustained during the extension for up to 72 weeks of the extension study (96 weeks from core baseline). After 96 weeks of imatinib treatment (Week 72 of extension), the mean improvement was 50 m (Figure 2). The mean improvement for ex-placebo patients at 72 weeks (72 weeks of imatinib) was 40 m.

The results of the final data set indicate that after 180 weeks of imatinib treatment (Week 156 of extension), the mean improvement was 73 m (Figure 3). The mean improvement for ex-placebo patients at 156 weeks (156 weeks of imatinib) was 30 m. However, these improvements could reflect the diminishing number of patients in the study at these later time points and a selection bias whereby patients experiencing measurable benefit were more likely to continue in study.

There was no clear difference overall between the 2 treatment groups for TTCW (Figure 4). Clinical worsening events occurred in 33 of 66 (50%) and 36 in 78 (46%) of ex-imatinib and ex-placebo patients, respectively, and 14 and 13 events, respectively, occurred in the core study, corresponding to event-free rates of 78.8% (ex-imatinib) and 83.3% (ex-placebo) at the start of the extension study. At Week 48, event-free rates were similar in ex-imatinib and ex-placebo patients (69.5% and 68.2%, respectively), whereas at Week 72, event-free rates were 58.3% and 62.9% in the ex-imatinib and ex-placebo patients, respectively. In the extension study, the most frequent clinical worsening events were hospitalization due to worsening of PAH and worsening of WHO FC (Table 4). Overall, approximately 30% of all patients had at least 1 unscheduled PAH-related hospitalization.

Of the 79 evaluable patients treated with imatinib for 96 weeks (ex-imatinib patients 24 weeks on core and 72 weeks on extension; ex-placebo patients 96 weeks on extension), 23 (29%) showed an improvement in WHO FC by 1 level or more, and 55 (70%) had stable WHO FC (Figure 5). This again tends to reflect a retention bias.

Discussion

There are now 14 commercially distinct drugs available for oral, intravenous, sub-cutaneous, or inhaled administration for the treatment of PAH.[2–15] These drugs target 3 main
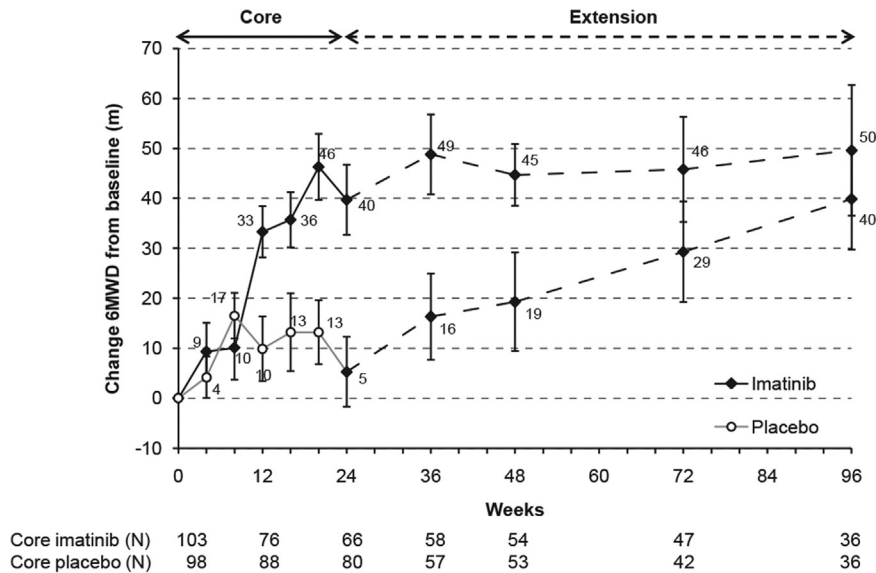
Figure 2 Change in 6-minute walk distance (6MWD) in meters from core study baseline (up to 72 weeks in the extension study). Data are mean ± standard error.

pathways involved in PAH disease onset and progression and appear to have improved patient survival from the pre-treatment era median of 2.5 years to a mean of about 5 to 7 years.[17,31] Because this is still an incurable disease with a poor outcome, it is important to consider new therapies targeting alternative pathways.

After in vitro and preclinical studies suggesting that imatinib therapy demonstrated a regression in obliterative vascular endothelial and smooth muscle proliferation,[32] the IMPRES study was undertaken. This demonstrated improvement in exercise capacity and PVR in severe PAH patients, as defined by marked elevation of PVR and persistent functional limitation despite therapy with 2 to 3 PAH-specific drugs.[28] However, that study failed to achieve important supporting end points, including TTCW, and also raised major questions about the safety and tolerability of imatinib in this high-risk patient population.[33] All patients who participated in the open-label extension were informed

of the risk of SDH, discussed this with their investigator/physician, and signed an Investigational Review Board amendment-approved reconsent detailing the risks of SDH.

In 2012, Novartis submitted a package of data in the PAH indication to regulatory authorities in the European Union, Switzerland, Japan, and the United States. After receiving feedback that additional data would be needed to secure marketing approval, these regulatory applications were withdrawn in 2013, followed by the decision to discontinue development of this indication for oral imatinib.

The data reported here provide uncontrolled extension study follow-up data, at the time the extension study was terminated, for patients who originally participated in the RCT. Of 144 patients who entered the extension study, 135 (93.8%) discontinued before completion, and 9 completed the extension study before study termination. The safety profile of imatinib in this extension study reflected the SAEs seen in the core trial; importantly, 8 cases of SDH were
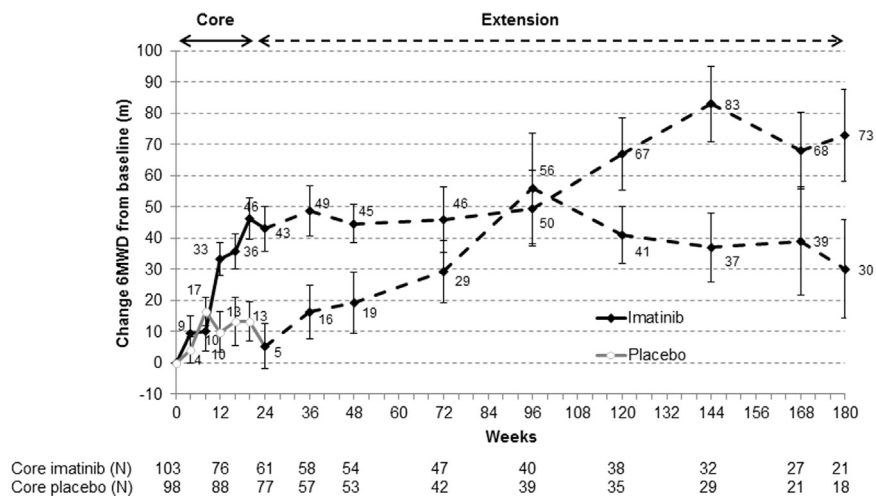
Figure 3 Change in 6-minute walk distance (6MWD) in meters from core study baseline (up to 156 weeks in the extension study). Data are mean ± standard error.
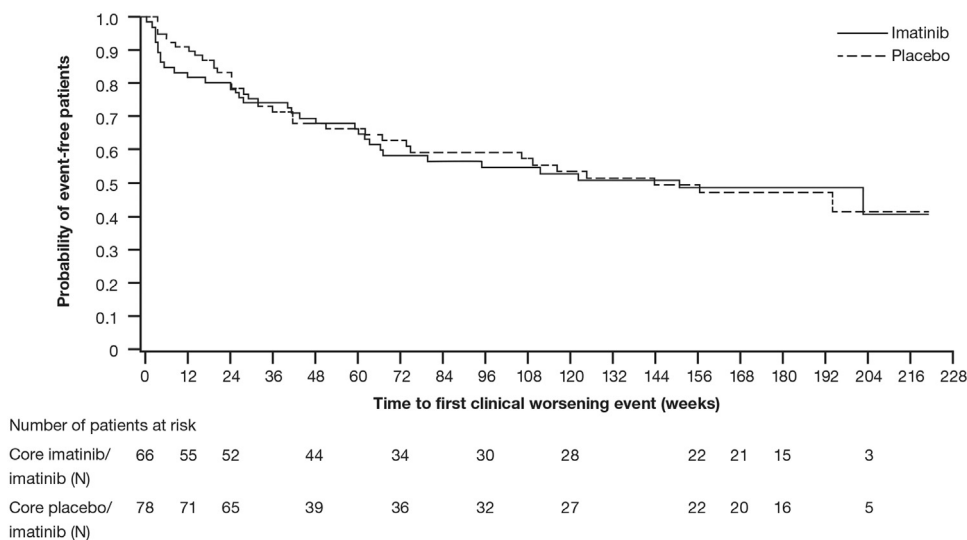
Figure 4 Time to first clinical worsening, adjudicated events, by core study treatment. Patients without an event were censored at the extension study completion visit or study discontinuation visit plus 30 days. Clinical worsening was defined as all-cause mortality, overnight hospitalization for worsening of pulmonary arterial hypertension (PAH), a worsening of World Health Organization (WHO) functional class by at least 1 level, or a 15% decrease in the 6-minute walk distance compared with baseline confirmed by two 6-minute walk tests at 2 consecutive study visits. Overnight hospitalization for worsening of PAH were adjudicated by an independent panel.

reported across the core and extension studies. Our review reveals no distinguishing phenotypic features of the patients who experienced SDH.

The recently described minimal clinically important difference in the 6MWT for PAH patients suggests that this value is approximately 33 m (range, 25.1–38.5 m).[34] Although conclusions in this extension study are hampered by a high discontinuation rate, the sustained improvement in the 6MWD seen in the limited number of patients continuing drug for up to 180 weeks exceeds this newly described minimal clinically important difference as well as that seen in the previously reported combination studies. These prior studies, however, had substantially higher patient retention. This suggests that those patients able to tolerate imatinib without disabling AEs or SAEs did demonstrate an improvement in a commonly used surrogate of efficacy—the 6MWT. Importantly, improvement in the 6MWD in the RCT IMPRES study did not translate into improvement in outcome as assessed by other measures of clinical outcome.

An important secondary end point of the IMPRES RCT study was reduction in PVR. A 30% reduction in PVR would be considered a clinically important reduction. In the RCT, 46 patients achieved a 30% reduction in PVR, and 43 of these patients entered the extension study, with 30 remaining in the study through the open-label data lock. This fact and the improved walk distance seen in those patients remaining in the study underscore the fact that the willingness of patients to remain in the extension was determined by their perceived benefits in function. It is possible that a biopsy specimen repository with subsequent genotyping may have better informed us about factors governing response and outcomes. This is an ongoing limitation to this and other studies in pulmonary hypertension.

Among the events included in the TTCW assessment in this study were death, adjudicated hospitalization for worsening PAH, or worsening of WHO FC by 1 level with

Table 4 Incidence of Clinical Worsening Events

Patients with clinical worsening events[a]	Ex-imatinib (n = 66) No. (%)	Ex-placebo (n = 78) No. (%)
Death	5 (8)	12 (15)
Hospitalization for worsening PAH	22 (33)	22 (28)
Worsening of WHO FC by ≥1 level	16 (24)	15 (19)
15% reduction in 6MWD[b]	8 (12)	15 (19)
and worsening of WHO FC by ≥1 level	1 (2)	3 (4)

6MWD, 6-minute walk distance; FC, functional class; PAH, pulmonary arterial hypertension; WHO, World Health Organization.
[a]Data are for all patients who entered the extension, irrespective of whether the event occurred during the core study or during the extension.
[b]On 2 consecutive occasions vs baseline.
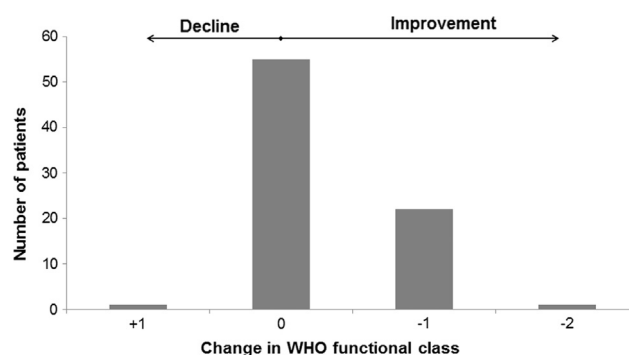
Figure 5 Change in World Health Organization (WHO) functional classification from core study baseline after 96 weeks of treatment with imatinib (n = 79 evaluable patients).

a reproducible 15% reduction in 6MWD. Based on the Kaplan-Meier estimates, the TTCW event-free rates in the extension were similar in the ex-imatinib and ex-placebo arms (70% vs 68%, 58% vs 63%, and 55% vs 59% at Weeks 48, 72, and 96, respectively). In the IMPRES extension, adjudicated hospitalizations for worsening PAH most frequently defined clinical worsening (33% and 28% of all causes of worsening), followed by deteriorating FC (24% and 19%) and walk distance (12% and 19%).

This extension study provides information about the effect and durability of benefits of imatinib in the treatment of complicated and sick PAH patients but is hampered by 3 major concerns. The first concern is the high dropout rate in the core study in the active treatment arm and, subsequently, in the ex-placebo patients receiving imatinib in the extension study. This biases any analyses because it selects for analysis those patients who are healthy/tolerant survivors.

The second concern relates to the lack of correlation between the 6MWT, the traditional PAH study end point, and TTCW, an increasingly relevant clinical index.

Finally, the occurrence of SDHs is a rare event in other studies of PAH. Central nervous system hemorrhage is a reported AE with imatinib, but the overall frequency of its occurrence in the studies of patients treated for malignancy (which included the intrathecal use of imatinib) is usually less than that observed in this study (0.2%–5.8%).[35] The rationale for central nervous system hemorrhage in studies of malignancy (tumor necrosis) cannot be invoked in imatinib-treated PAH patients. SDHs occurring only in those on anti-coagulation would be reasonably addressed by avoiding the combination of these 2 therapies. This approach however, completely ignores underlying causation and the fact that anti-coagulation (Table 1) was no more frequent in this study than in other short-term and long-term pharmaceutical trials in PAH, where SDHs are so rare as not to be included in reports of SAEs. Additional limitations of the extension study include:

1. Lack of blinding
2. Lack of control group
3. Absence of survival data in those patients who prematurely discontinued the study.

In addition, some patients clearly had robust improvements in walk distance and (in the RCT) in PVR and hence remained in the study, although this did not correlate with a reduction in clinical worsening events.

In conclusion, SAEs and safety concerns preclude the use of imatinib in the treatment of PAH. The possibility, however, that this drug or similar drugs may be capable of producing substantial disease modification should not be dismissed. Similar to other diseases, such as neoplasia and connective tissue diseases, where anti-proliferative drugs are effectively used, any potential benefit may be restricted to a small or specific sub-set of patients, which underscores the need for biobank repository in subsequent studies of novel or complex

therapies. Most of the patients enrolled in the study were intolerant of the drug and experienced no benefit or experienced an SAE. In a minority of patients originally enrolled and remaining in the study, imatinib did appear to produce a substantial and durable improvement in the walking distance. As in the original RCT, however, this did not translate into freedom from clinical worsening. Off-label use of imatinib in PAH patients is not supported by these data.

Disclosure statement

Supplementary data

Supplementary data are available in the online version of this article at www.jhltonline.org.

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