PBI-1402 increases hemoglobin level and red blood cell count in chemotherapy-induced anemia

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Abstract

BACKGROUND
PBI-1402 is a novel orally active low molecular weight synthetic compound with erythropoiesis stimulating activity. PBI-1402, via a mechanism of action distinct from erythropoietin (EPO), promotes the differentiation of immature stem cells in CFU-GEMM and subsequent maturation to BFU-E leading to reticulocyte and erythrocyte production. A clinical phase I study demonstrated that PBI-1402 induced a significant increase (100%, p < 0.0001, compared to placebo) of relative and absolute reticulocyte count in healthy volunteers after 21 days of oral treatment and was devoid of significant side effects.

AIMS
The objectives of this phase Ib/II trial were to study the safety and tolerability of PBI-1402 and to assess its biological efficacy on hemoglobin (Hb) level and red blood cell (RBC) count in patients with chemotherapy-induced anemia (CIA).

METHODS
Three cohorts of six patients received 8 weeks of treatment with PBI-1402 administered per os once a day, at three different doses (44, 66 and 88 mg/kg), and were monitored every two weeks for safety, tolerability, Hb level, RBC count and clinical biochemistry. Patients remained on their chemotherapy during PBI-1402 treatment.

RESULTS
Seventeen patients completed their 8-week PBI-1402 treatment. One patient withdrew consent at week 4. PBI-1402 was well tolerated and no severe side effects were observed. Mean increases of Hb level were highest at week 4 to 6 for the 88 mg/kg group and highest at week 8 for the 44 and 66 mg/kg groups. For all treatment groups, a statistically significant increase in mean Hb level was observed at week 8 (p = 0.03). Mean increases of RBC were also highest at week 4 to 6 for the 88-mg/kg group and highest at week 8 for the 44 and 66 mg/kg groups. One patient required a blood transfusion. Overall, after 8 weeks of oral PBI-1402 treatment, Hb level and RBC were increased in 69% of the patients with a significant p value of 0.031 and 0.036, respectively.

CONCLUSION
Oral treatment with PBI-1402 offers the potential for a novel therapy of CIA. In addition, PBI-1402 is safe and well tolerated.

Background

PBI-1402 increases the production of immature progenitor stem cells from bone marrow and promotes the maturation of BFU-E. These effects result in an increase of production of RBC in two animal models: immunosupressed mice and 5/6 nephrectomized rats. Furthermore, in a phase I clinical trial, PBI-1402 increased significantly both the relative and absolute numbers of reticulocytes in healthy volunteers. These data suggest that PBI-1402 may be a drug candidate to treat anemia. Anemia is one of the most serious side effects caused by chemotherapy, with bone marrow suppression being the major contributing factor. The first line treatment of patients with chemotherapy-induced anemia (CIA) is rhEPO, which is active in only 50-60% of CIA patients. Data demonstrate that an orally active small molecule can stimulate erythropoiesis and ameliorate hematology parameters in CIA patients.

Methods

This phase Ib/II trial has been conducted in Eastern Europe under the supervision of Pharm-Olam International Ltd., a US-based clinical research organization. Patients recruited were anemic as a result of chemotherapy and their chemo-therapy treatment continued throughout the duration of this trial. The trial design included three cohorts of six patients at three doses (44, 66 and 88 mg/kg). The end parameters (Hb, RBC and Ht) were compared against each patient's baseline value at entry.

Summary of protocol

PRIMARY END POINT
Safety and tolerability of PBI-1402.

SECONDARY END POINT
Biological efficacy of PBI-1402 on Hb, RBC and Ht. Reduction in transfusions.

INCLUSION CRITERIA
Hb between 90 and 110 g/L, adequate hepatic and renal functions.

EXCLUSION CRITERIA
Patients with anemia due to folate and vitamin B12 deficiency, hemolysis, bleeding, or active infection. Patients who have received rhEPO within eight weeks before baseline evaluation, or two+ RBC transfusions (4 weeks), or any RBC transfusion (2 weeks).

STUDY PROTOCOL
Three cohorts of six CIA patients received eight weeks of oral treatment with PBI-1402 once a day, at three doses (44, 66 and 88 mg/kg). Monitoring every two weeks for Hb level, RBC count, Ht, blood chemistry and adverse events.

Results

Seventeen CIA patients have completed an 8-week oral treatment with PBI-1402. One patient withdrew consent at week 4. Patients remained on their chemotherapy during PBI-1402 treatment. One patient needed transfusion and was excluded from the efficacy analysis. Five patients reported side effects deemed related to PBI-1402 treatment. These side effects were of low grade. No meaningful changes in blood chemistry and urinalysis were noted.

Table 1 **Number of adverse events related to PBI-1402 reported by five patients**

ADVERSE EVENTS	NUMBER OF EPISODES
Oesophagitis	2
Dyspepsia	4
GI discomfort	2
Metal taste / Burning sensation	3
Heartburn	3

Table 2 **Summary of the biological efficacy of PBI-1402 in patients that completed the study**

PATIENTS	NUMBER	%
Completed the study	17	
Not requiring transfusion	16	94
Evaluated patients	16	
Increase in Hb	11	69

Table 3 **Hemoglobin level of all patients after treatment**

Hb LEVEL (g/dL) AFTER TREATMENT	% OF PATIENTS
> 10	68
> 10.5	56
> 11	25
< 9	6

PBI-1402 induces a significant increase in hemoglobin level at week 8.

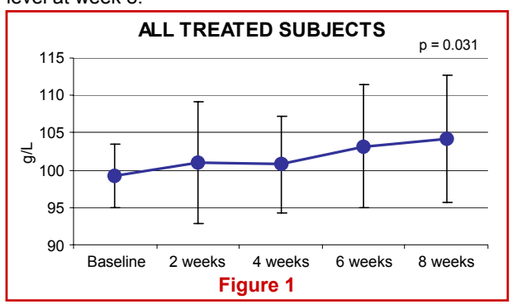

Figure 1

PBI-1402 induces a significant increase in RBC at week 8 in responders. PBI-1402 stabilizes RBC count in non-responders.

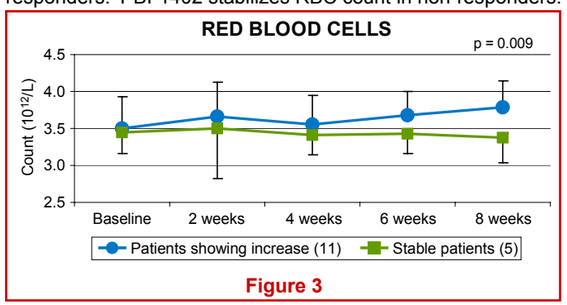

Figure 3

PBI-1402 induces a significant increase in Hb at week 6 and 8 in responders. A small decrease of Hb level is observed in non-responders.

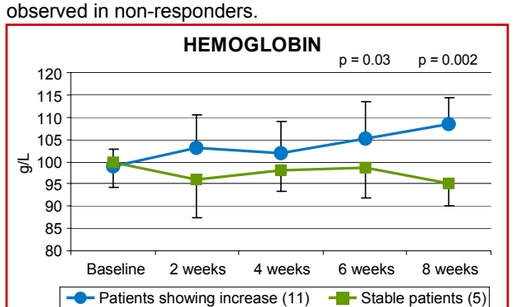

Figure 2

PBI-1402 induces a significant increase of hematocrit value at week 6 and 8 in responders and no significant change is observed in non-responders.

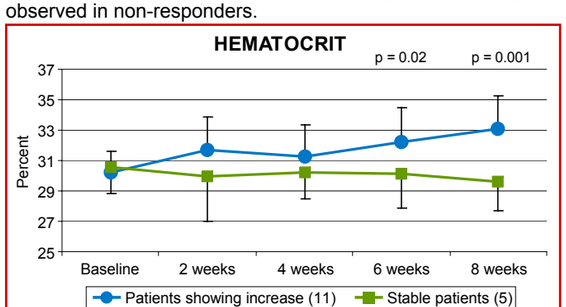

Figure 4

Conclusion

PBI-1402 offers the potential for a novel therapy of anemia. PBI-1402 strengths are:

➔ **TOLERABILITY**
Phase I: 36 healthy individuals.
Phase Ib/II: 18 CIA subjects side effects do not appear to be related to the dose.

➔ **ORAL ACTIVITY**
Increase of Hb level, RBC and Ht in CIA subjects.
Reduction in transfusions.
Convenience of oral therapy in CIA patients.

➔ **REDUCED COST**