POSTER 1990

Pharmacokinetics and Exposure–Response of Luspatercept in Patients With Anemia Due to Low- or Intermediate-1-Risk Myelodysplastic Syndromes (MDS): Preliminary Results From Phase 2 Studies

Nianhang Chen[1], Abderrahmane Laadem[1], Dawn M. Wilson[2], Xiaosha Zhang[2], Matthew L. Sherman[2], Steve Ritland[1], Kenneth M. Attie[2]

[1]Celgene Corporation, Summit, NJ; [2]Acceleron Pharma, Cambridge, MA; USA

INTRODUCTION

- Myelodysplastic syndromes (MDS) are a heterogeneous group of diseases characterized by ineffective erythropoiesis leading to anemia[1]
- Luspatercept (ACE-536) is a modified activin type IIB receptor that acts as a ligand trap to block inhibitors of late-stage erythropoiesis in the TGF-β superfamily[2]
- In phase 2 studies, luspatercept led to increases in hemoglobin (Hb) levels and reductions in transfusion burden in patients with International Prognostic Scoring System (IPSS)-defined Low- or Intermediate-1-risk MDS[3]

OBJECTIVE

- To characterize the pharmacokinetics of luspatercept and to explore the exposure–response relationship for efficacy and safety in patients with IPSS-defined lower-risk MDS, thereby informing selection of the starting dose in phase 3 studies of luspatercept in MDS

METHODS

Study Design

- Pharmacokinetics, safety, and efficacy data were collected from two phase 2 studies (base and extension; NCT01749514 and NCT02268383) of luspatercept for the treatment of anemia in patients with IPSS-defined lower-risk MDS
- Patients were categorized by baseline transfusion burden:
  - Patients requiring < 4 red blood cell (RBC) units in the 8 weeks prior to study start and with baseline Hb < 10 g/dL were classified as low transfusion burden (LTB)
  - Patients requiring ≥ 4 RBC units in the 8 weeks prior to study start were classified as high transfusion burden (HTB)

Treatment

- In the base study, luspatercept was administered by subcutaneous injection once every 3 weeks, for up to 5 doses, to sequential cohorts
- The base study included:
  - A dose-escalation phase, with fixed doses ranging from 0.125 mg/kg to 1.75 mg/kg
  - An expansion cohort, with a starting dose of 1.0 mg/kg followed by individual dose titration up to 1.75 mg/kg
- Patients completing the base study were eligible to enroll in an extension study, where patients continued to receive luspatercept once every 3 weeks for up to 5 years
- Patients who experienced treatment interruption for ≥ 3 months before enrolling in the extension study received a starting dose of 0.8 mg/kg, followed by dose titration, and were treated as "new" patients in the exposure–response analysis

Study Endpoints

- The main exposure endpoint was area under the luspatercept serum concentration–time curve (AUC)
- Clinical endpoints included Hb level increase, transfusion reduction, and drug-related adverse events (AEs) in weeks 1–15
- Responders were defined as patients achieving erythroid hematologic improvement (HI-E) per International Working Group (IWG) criteria:[4]
  - For LTB patients, a Hb increase of ≥ 1.5 g/dL sustained for 8 weeks
  - For HTB patients, a transfusion reduction of ≥ 4 RBC units over 8 weeks

RESULTS

Patients

- As of July 20, 2016, preliminary data were available for 66 patients:
  - 22 LTB patients (baseline Hb levels 6.4–10.1 g/dL)
  - 44 HTB patients (baseline transfusion burden 4–18 units/8 weeks)
- Median age was 72 years (range 27–90) and 41% of patients were female
- Of 39 patients eligible for individual dose titration:
  - 49% experienced ≥ 1 dose escalation (to 1.33 mg/kg) in the first 3 months
  - 15% experienced 2 dose escalations (to 1.75 mg/kg) in the first 3 months

Pharmacokinetics

- Luspatercept pharmacokinetics were adequately described by a one-compartment model with linear absorption and elimination
  - Dose-dependent increases in serum drug exposure (AUC and C_{max}) are shown in Table 1
  - Half-life of luspatercept in serum was approximately 10–14 days across doses (Table 1)

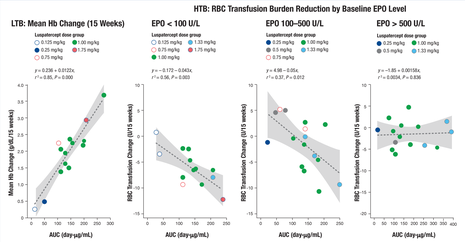
Table 1. Summary of Luspatercept Pharmacokinetic Parameters in the Base Study

Parameter[a]	0.125 mg/kg (n = 3)	0.25 mg/kg (n = 3)	0.50 mg/kg (n = 3)	0.75 mg/kg (n = 6)	1.0 mg/kg (n = 3)	1.33 mg/kg (n = 6)	1.75 mg/kg (n = 3)	Expansion 1.0 mg/kg (n = 31)
K_a, 1/day	0.16 (89)	0.32 (70)	0.47 (229)	1.02 (105)	0.38 (178)	0.35 (69)	0.41 (243)	0.45 (116)
T_{max}, days	9 (8–15)	6 (6–7)	6 (2–10)	2 (2–8)	5 (3–10)	6 (4–12)	6 (2–10)	6 (2–10)
C_{max}, μg/mL	0.66 (30.0)	0.92 (79.6)	2.49 (30.1)	4.64 (48.2)	4.67 (14.4)	8.47 (21.9)	10.4 (18.2)	6.16 (29.2)
AUC, day·μg/mL	24.7 (60.8)	25.9 (59.1)	72.7 (39.6)	117 (37.0)	102 (29.7)	239 (43.6)	235 (10.6)	148 (30.8)
$t_{1/2}$, days	14.4 (47.9)	12.1 (110.0)	14.0 (45.8)	14.7 (32.6)	8.9 (48.7)	13.8 (41.4)	9.71 (27.1)	11.3 (43.7)
CL/F, mL/day	340 (46.4)	751 (84.8)	455 (47.9)	486 (36.3)	831 (31.5)	431 (41.4)	596 (10.3)	512 (32.5)
V/F, L	7.1 (36.0)	13.1 (187.3)	9.2 (38.9)	10.3 (21.6)	10.7 (51.2)	8.6 (27.0)	8.3 (16.5)	8.3 (38.6)

[a] Data are expressed as median (range) for T_{max} and as geometric mean (coefficient of variation, %) for the other parameters; all parameters are estimated by fitting multiple-dosing concentration data to a one-compartment linear model.

AUC, area under the curve; CL/F, clearance; C_{max}, maximum serum concentration; K_a, absorption rate constant; $t_{1/2}$, serum half-life; T_{max}, time to C_{max}; V/F, volume of distribution.

Figure 1. Serum Drug Exposure Versus Hb Increase in LTB Patients and RBC Transfusion Burden Reduction in HTB Patients by Baseline EPO Level



Shaded area represents 95% confidence interval for predicted mean.

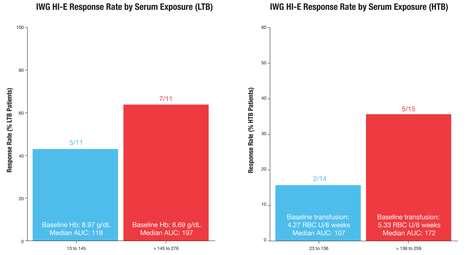
AUC, area under the curve; EPO, erythropoietin; Hb, hemoglobin; HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell.

- Body weight (Wt) positively correlated with luspatercept clearance and its volume of distribution ($P < 0.01$) in population pharmacokinetics analysis, supporting weight-based dosing
  - Clearance (L/day) = $0.544 \times (Wt/78)^{0.813}$
  - Volume of distribution (L) = $10.5 \times (Wt/78)^{0.903}$
- Baseline transfusion burden (i.e. LTB vs HTB) and erythropoietin (EPO) level had no significant effect on luspatercept pharmacokinetics

Relationship Between Serum Exposure and Efficacy

- Increase in luspatercept serum AUC was approximately proportional to dose (Table 1)
- Among LTB patients who were transfusion-free on treatment, higher luspatercept AUC correlated with greater Hb increase ($P = 0.001$) (Figure 1)
- Among HTB patients, AUC correlated with transfusion burden reduction in patients with baseline EPO ≤ 500 U/L ($P < 0.01$) (Figure 1) but not in patients with baseline EPO > 500 U/L
- Luspatercept AUC correlated with rate of IWG HI-E responders for LTB patients, HTB patients with baseline EPO ≤ 500 U/L (Figure 2), and the 2 groups combined (Figure 3)

Figure 2. Response Rate by Exposure in Weeks 1–15 for LTB and HTB Patients



HTB patients with baseline erythropoietin > 500 U/L were excluded. Median AUC was used as a cut-off to divide patients into 2 groups for analysis (≤ median AUC and > median AUC).

AUC, area under the curve; Hb, hemoglobin; HI-E, erythroid hematologic improvement; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion with burden; RBC, red blood cell.

Figure 3. Overall Rate of IWG HI-E Response Versus Luspatercept Serum Exposure

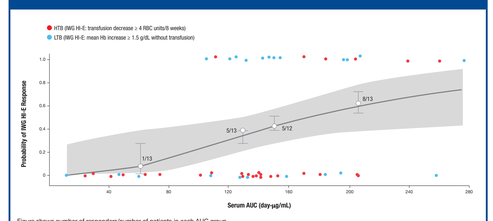


Figure shows number of responders/number of patients in each AUC group.

AUC, area under the curve Hb, hemoglobin; HI-E, erythroid hematologic improvement; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell.

Predictors of RBC-Transfusion Independence

- Among patients with a transfusion requirement of ≥ 2 RBC units/8 weeks and baseline EPO ≤ 500 U/L:
  - Baseline transfusion burden was a significant predictor of achieving RBC transfusion independence (RBC-TI) ≥ 8 weeks (Table 2)
  - Higher AUC was associated with greater rates of RBC-TI ≥ 8 weeks after accounting for baseline transfusion burden (Table 2)

Relationship Between Serum Exposure and Adverse Events

- There was no apparent relationship between luspatercept serum exposure and severity or frequency of drug-related AEs (Figure 4)

Phase 3 Starting Dose and Target AUC

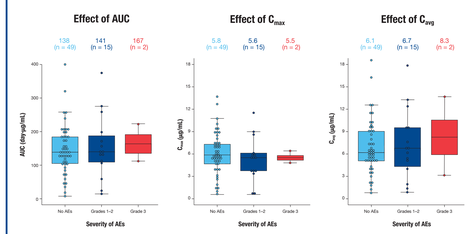
- Population pharmacokinetics simulation predicted that:
  - A starting dose of 1.0 mg/kg would result in 90% of LTB patients achieving target AUC (123 day·μg/mL) for HI-E (Figure 5)
  - A starting dose of 1.1 mg/kg would result in 50% of HTB patients achieving target AUC (157 day·μg/mL) for HI-E (Figure 5)
  - A higher dose may be required in some patients to achieve target AUC associated with a reduction in transfusion burden of ≥ 4 RBC units/8 week

Table 2. Predictors of RBC-TI ≥ 8 Weeks Among Patients With a Transfusion Requirement ≥ 2 RBC U/8 Weeks and Baseline EPO ≤ 500 U/L

Predictor of RBC-TI	Odds Ratio (95% CI)	*P* value
Luspatercept serum AUC	1.02 (1.00–1.04)	0.045
Ln(Baseline transfusion burden)	0.047 (0.002–0.326)	0.0004

AUC, area under the curve; CI, confidence interval; EPO, erythropoietin; RBC, red blood cell; TI, transfusion independence.

Figure 4. Relationship Between Drug-Related AEs and Luspatercept Serum Exposure



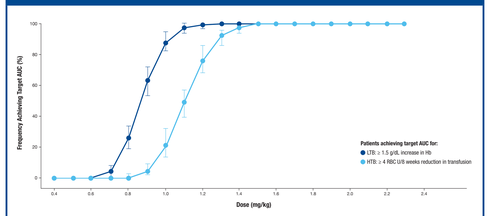
	Mean AUC, day·μg/mL	Frequency of AEs, number of patients (%)		
		No AEs	Grades 1–2	Grade 3[a]
AUC ≤ 139 day·μg/mL (n = 33)	105	25 (75.8)	7 (1.2)	1 (3.0)
AUC > 139 day·μg/mL (n = 33)	184	24 (72.8)	8 (24.2)	1 (3.0)

[a] Two grade 3 AEs were reported; 1 in the low-AUC group and 1 in the high-AUC group. No grade 4 AEs were reported.

AE, adverse event; AUC, area under the curve; C_{avg}, average serum concentration; C_{max}, maximum serum concentration.

RESULTS (cont)

Figure 5. Predicted Frequency of Patients Achieving Target Luspatercept Serum AUC at Various Dose Levels



AUC, area under the curve; Hb, hemoglobin; HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell.

CONCLUSIONS

- Higher luspatercept serum exposure was found to correlate with greater rates of IWG HI-E for both LTB and HTB patients
- Exposure–response modeling and pharmacokinetic simulation support the use of a starting dose of 1.0 mg/kg, with intra-patient dose escalation up to 1.75 mg/kg according to HI-E response
- A phase 3 study of luspatercept in regularly transfused ring sideroblast-positive patients with Revised IPSS Very Low-, Low-, or Intermediate-risk MDS is ongoing (the MEDALIST study; ClinicalTrials.gov identifier: NCT02631070)

REFERENCES

1. Fenaux P, Ades L. *Blood*. 2013;121(21):4280-4286.
2. Attie KM, Allison MJ, McClure T, et al. *Am J Hematol*. 2014;89(7):766-770.
3. Platzbecker U, Giagounidis A, Germing U, et al. *Haematologica*. 2016;101(S1):abstract S131.
4. Cheson BD, Greenberg PL, Bennett JM, et al. *Blood*. 2006;108(2):419-425.

ACKNOWLEDGEMENTS

This study was sponsored by Celgene Corporation, Summit, NJ and Acceleron Pharma, Cambridge, MA, USA. The authors received editorial assistance and printing support in the preparation of this poster from Excerpta Medica (James O'Reilly, PhD), supported by Celgene Corporation. The authors are fully responsible for all content and editorial decisions.

CORRESPONDENCE

Nianhang Chen – nchen@celgene.com

DISCLOSURES

N.C., A.L., S.R.: Celgene Corporation – employment, equity ownership. D.M.W., K.M.A.: Acceleron Pharma – employment, equity ownership. X.Z.: Acceleron Pharma – employment. M.L.S.: Acceleron Pharma – employment, equity ownership, patents and royalties.

Trial Registry: NCT01749514 and NCT02268383