Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-333/SE5-008
Brand Name:	Agrylin®
Generic Name:	Anagrelide HCl
Dosage form and Strength:	0.5 and 1.0 mg capsules
Route of Administration:	Oral
Indication:	For the treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events.
Sponsor:	Shire Pharmaceutical Development Inc.
Type of Submission:	Pediatrics Study Report
Clinical Division:	GI and Coagulation (HFD-180)
OCPB Division:	HFD-870/DPE II
Priority:	Priority (6 months)
Submission Date:	03/12/04, 05/10/04
OCPB Consult Date:	03/15/04
Reviewer:	Tien-Mien Chen, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.

I. Executive Summary

The pediatric study report was submitted on 03/12/04 for Agrylin (anagrelide HCl). Study SPD422-202 was a Phase II, randomized, open-label, single-arm, multiple-center, safety, pharmacokinetic (PK) and pharmacodynamic (PD) study conducted in 18 adults/adolescents (A/A patient group; ? 16 years old) and in 17 pediatrics/adolescents (P/A patient group; < 16 years old). The evaluations for PK, PD (reduction in platelet counts), and cardiovascular monitoring for safety assessment related to the vasodilatory and positive inotropic effects of anagrelide and its active metabolite BCH24426 were obtained on Day 30 for analysis.

Between-group comparisons for the entire PK dataset when normalized to 1 mg and a body weight of 70 kg showed that the systemic exposure, C_{max} and AUC_{0-t} of anagrelide was substantially lower in P/A patient group than in A/A patient group. The reduced exposure to anagrelide in the P/A patient group could be partly due to a higher metabolic function in younger patients (mean: 11.4 years old) compared to that in A/A patient group (mean: 63.4 years old). However, no differences in exposure to the active metabolite (BCH24426) were found.

For PD, **1)** decreases in platelet counts were significantly correlated with anagrelide and BCH24426 based on entire data from the study and **2)** significant positive correlations were identified between increases in heart rate and corresponding C_{max} of anagrelide and BCH24426. However, no apparent correlation was found between diastolic blood pressure decreases and corresponding C_{max} of anagrelide and BCH24426.

Regarding analyses on total daily starting dose and dose adjustments, there appeared to be no differences in the dosing between P/A and A/A patient groups.

Overall, sponsor recommends adult dosing administration guidelines to pediatrics as well and it appears reasonable.

A. Recommendations

The Supplement SE5-008 to NDA 20-333 is acceptable from the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) viewpoint provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

B. Phase IV Commitments: None

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

On 11/26/02, Shire submitted the proposed pediatric study request (PPSR) for Agrylin. A pediatric exclusivity written request (PEWR) was issued on 03/27/03 and subsequently several amendments were made. In this submission, results from study SPD422-202 were submitted to fulfill the requirements of PEWR. The PEWR called for a single study to determine safety, PK, and PD of agrylin in pediatric subjects.

Study SPD422-202 was a randomized, open-label, single-arm, multiple-center, safety, PK, and PD study conducted in 18 adults/adolescents (A/A patient group; ? 16 years old) and in 17 pediatrics/adolescents (P/A patient group; < 16 years old). On Day 30 of treatment, evaluations for PK, reduction in platelet counts, safety assessment related to the vasodilatory and positive inotropic effects were obtained. Because the blood sampling scheduled for PK on a 7-year-old pediatric female patient (No. 14-002) could not be obtained due to viral infection, the PK and PD data were obtained from 7 out of 8 patients in the <12 year old age group. Each patient group contained 3 subgroups depending on dosing status at entry, i.e., anagrelide naïve patients, patients in titration phase, and anagrelide experienced patients. Overall, six naïve patients were recruited (5 in A/A patient group and 1 in P/A patient group) with others already on anagrelide treatment.

Plasma levels of anagrelide, active metabolite BCH24426 (or 3-OH), and inactive metabolite RL603 were obtained and analyzed. Only the PK of anagrelide and BCH24426, were employed to explore the potential relationship between plasma exposure with reduction of platelet count from baseline (PD) and heart rate and systolic/diastolic blood pressure (safety). The retrospective data on anagrelide starting dose, dose adjustment to maintain platelet counts, and adverse events (AE) were also analyzed for correlation.

Between-group comparisons for **1)** entire PK data set when normalized to 1 mg and a body weight of 70 kg and **2)** a subgroup dataset based only on patients receiving 0.5 mg BID showed that the systemic exposure, C_{max} and AUC_{0-t} of anagrelide was substantially lower in P/A patient group than in A/A patient group. The reduced exposure to anagrelide in the P/A patient group could be partly due to a higher hepatic function in younger patients (mean: 11.4 years old) compared to that in A/A patient group (mean: 63.4 years old) under the assumption of the same or similar bioavailability (F) value between two patient groups. No differences in exposure to the active metabolite (BCH24426) were found.

For PD, 1) decreases in platelet count were significantly correlated with anagrelide and its active metabolite (BCH24426) based on entire data from the study and 2) significant positive correlations were identified between increases in heart rate and corresponding C_{max} of anagrelide and BCH24426. However, no apparent correlation was found between diastolic blood pressure decreases and corresponding C_{max} of anagrelide and BCH24426.

Regarding analyses on total daily starting dose and on dose adjustments, there appeared to be no differences in the dosing between P/A and A/A patient groups.

Overall, sponsor recommends adult dosing administration guidelines to pediatrics as well.

IV. Question Based Review

A. General Attributes

Agrylin was approved on 03/14/97. It is indicated for the treatment of patients with thrombocythemia, secondary to myeloproliferative disorders (MPD), to reduce the elevated platelet count and the risk of thrombosis, and to ameliorate associated symptoms including thrombo-hemorrhagic events. The treatment should be initiated under close medical supervision. The recommended starting dosage of Agrylin® is 0.5 mg QID or 1 mg BID, which should be maintained for at least one week. Dosage should then be adjusted to the lowest effective dosage required to reduce and maintain platelet count below 600,000/µL, and ideally to the normal range. The dosage should be increased by not more than 0.5 mg/Day in any one week. Dosage should not exceed 10 mg/Day or 2.5 mg in a single dose.

B. General Clinical Pharmacology

The PK objective of Study SPD422-204 was to assess steady-state PK profile of anagrelide and its metabolites in P/A patient group and to compare with those in A/A patient group. The PD objectives were to **1)** evaluate the correlations if any, between anagrelide daily dose, resultant anagrelide plasma PK data and platelet counts between P/A and A/A patient groups and **2)** explore any relationship between heart rate and blood pressure and PK data of anagrelide and its metabolites.

PK Analysis:

Q1: Are PK parameters similar between P/A and A/A patient groups?

The dosing regimens employed in Study SPD422-202 are shown below:

Table 1. Dosing Regimen on Day 30

Subject Group	Frequency	Number of Subjects: Reference Dose (mg) 0.5	1.0	1.5	2	3	4
AA	qd	3	1				
	bid	4	3	1	1*		1[‡]
	tid	4					
	qid						
PA	qd			1			
	bid	6	1			1	
	tid		3[†]	2			
	qid	1	1				

AA: Adolescent/adult; PA: Pediatric/adolescent

* This subject on a bid regimen of 2mg in the morning, followed by an afternoon/evening dose of 1.5mg.

† One subject received three doses daily, but as follows: 1mg in the morning, 0.5mg in the afternoon, 1mg in the evening.

‡ This subject on a bid regimen of 4mg in the morning, followed by an afternoon/evening dose of 3mg.

Source: Section 16.3 of CSR, Listing 7.1, Listing 7.4

Since different dosing regimens were employed, a direct comparison between A/A and P/A patient groups was only possible based on a regimen of 0.5 mg BID. The PK parameters for the 0.5 mg BID dosing regimen are shown below in Table 2:

Table 2. Plasma levels obtained from direct comparison based on 0.5 mg BID Dosing Regimen (n=4 in A/A patient group and n=6 in P/A patient group)

PK Parameter	Anagrelide AA (n=4) Mean (SD)	Anagrelide PA (n=4-6) Mean (SD)	BCH24426 AA (n=4) Mean (SD)	BCH24426 PA (n=4-6) Mean (SD)	RL603 AA (n=4) Mean (SD)	RL603 PA (n=3-6) Mean (SD)
T_{max} (h)	1.9 (1.5)	3.9 (3.1)	2.4 (1.1)	4.0 (3.1)	3.1 (2.4)	2.8 (4.6)
C_{max} (ng/mL)	3.1 (1.3)	1.9 (0.6)	4.5 (1.8)	5.5 (2.8)	1.3 (0.5)	0.4 (0.2)*
C_{min} (ng/mL)	0	0.03 (0.04)	0.2 (0.1)	0.4 (0.2)	0.6 (0.5)	0.1 (0.0)
AUC_t (ng.h/mL)	8.6 (3.3)	8.2 (3.3)	19.9 (3.7)	24.4 (8.3)	10.0 (5.2)	3.0 (1.5)*
$T_{1/2z}$ (h)	1.5 (0.5)	3.9 (3.7)	2.8 (0.7)	4.2 (1.6)	11.0 (7.4)	4.5 (1.6)
C_{avg} (ng/mL)	0.7 (0.3)	0.7 (0.3)	1.7 (0.3)	2.0 (0.7)	0.8 (0.4)	0.2 (0.1)*
FI	4.3 (1.0)	3.2 (2.2)	2.5 (0.6)	2.6 (1.5)	1.1 (0.9)	1.0 (0.3)
Cl/F (mL/min)	1062 (315)	1169 (465)	429 (71)	373 (116)	1004 (455)	3245 (1301)*

AA. Adolescent/adult subject group: PA: Pediatric/adolescent subject group.

AA vs PA: *P<0.02

Source: Section 16.1.9.3 Table 2.1, Table 2.2, Table 2.3

A decrease in the mean C_{max} (39% ?) of anagrelide was seen between the two patient groups.

A further comparison of PK data normalized to a dose of 1 mg and a bodyweight of 70 kg for all subjects using all dosing regimens was made. The results are shown in Table 3.

Table 3. Plasma levels obtained from All Patients Employing All Dosing Regimen

PK Parameter	Anagrelide AA (n=15-18) Mean (SD)	Anagrelide PA (n=14-16) Mean (SD)	BCH24426 AA (n=17-18) Mean (SD)	BCH24426 PA (n=13-16) Mean (SD)	RL603 AA (n=11-18) Mean (SD)	RL603 PA (n=10-16) Mean (SD)
T_{max}	2.0 (1.4)	2.7 (2.2)	2.3 (1.2)	2.9 (2.2)	3.8 (2.9)	2.7 (3.0)
C_{max}	6.2 (3.8)	3.0 (1.3)#	8.7 (3.3)	7.7 (2.9)	3.2 (2.3)	1.1 (0.9)†
C_{min}	0.1 (0.2)	0.1 (0.1)	0.7(0.5)	0.8 (0.8)	1.3 (1.0)	0.3 (0.2)*
AUC_{τ}	19.5 (13.1)	10.8 (5.1)#	44.1 (17.8)	35.4 (15.3)	32.1 (32.9)	6.4 (4.0)‡
$T_{1/2z}$	1.7 (0.8)	2.3 (2.4)	3.9 (1.7)	3.3 (2.4)	8.7 (4.8)	6.6 (2.9)
C_{avg}	1.4 (1.0)	1.0 (0.5)	3.1 (0.9)	3.3 (1.7)	2.2 (1.6)	0.6 (0.4)†
FI	4.8 (2.8)	3.4 (2.2)*	2.8 (1.3)	2.4 (1.3)	1.2 (1.0)	1.4 (1.1)
Cl/F	1130 (525)	1828 (699)#	436 (178)	565 (263)	1104 (1019)	3815 (2370)‡

$ Drug concentrations were normalized to a dose of 1mg and a bodyweight of 70kg.
AA: Adolescent/adult subject group: PA: Pediatric/adolescent subject group.
AA vs PA: *p<0.02; #p<0.005 †p<0.001; ‡p<0 0001
Source: Section 16.1.9.3, Table 3.1, Table 3.2, Table 3.3

The sponsor concluded that;

1) Exposure to anagrelide was significantly lower in P/A patient group (mean C_{max} 52% ? and AUC_{0-t} 45% ?) compared to that of A/A patient group (p=0.0021 and p=0.0047, respectively),
2) No significant differences in mean C_{max} and AUC_{0-t} for BCH24426 were found,
3) The mean anagrelide Cl/F was 62% greater in P/A patient group than in A/A patient group (p=0.0047), and
4) The mean ratios of normalized (dose/weight) AUC_{0-t} for anagrelide: BCH24426: RL603 were reported to be 1.0:2.3:1.6 for A/A patient group and 1.0:3.3:0.6 for P/A patient group indicating that there is a higher systemic exposure of the active metabolite, BCH24426 in the P/A patient group than that in A/A patient group.

The sponsor speculated that these findings may be attributable to a higher hepatic and renal function of younger P/A patient group under the assumption of the same or similar F value between two patient groups.

PK/PD Analysis:

Q2: Are there correlations between reduction of platelet counts and plasma PK data in P/A and/or in A/A patient group and between changes of heart rate and blood pressure and plasma PK data of anagrelide and its metabolites?

General assessments of the safety finding of this study are deferred to the reviewing Medical Officer. The following is a discussion of the potential correlations between PK parameters and PD (and safety) parameters.

Correlations in patient groups with apparent association between the exposure, C_{max} of anagrelide or BCH24426 and maximal change in diastolic blood pressure were explored. The results are shown below in (Tables 4 and 5):

Table 4. Correlation Between Anagrelide C_{max} and Maximal Change in Diastolic Blood Pressure

Subject Group (n=15)	Subject Number	Maximal Change in Diastolic BP (mmHg)	Time of Maximal BP Change (h)	Anagrelide C_{max} (ng/mL)	Time of C_{max} (h)
Adolescent/Adult	03-002	34	4	5.4	4
	03-003	40	1.5	5.3	1
	03-006	12	1	3.1	4
	07-001	16	2	4.9	0.5
	07-002	20	1	5.7	0.5
	07-003	27	0.5	3.9	4
	07-004	18	2	2.6	1.5
	07-005	16	2	1.3	2
	10-002	12	8	3.3	1
	10-004	20	6	2.9	4
	11-001	23	2	25.5	1
Pediatric/Adolescent	14-001	20	1.5	5.7	2
	20-001	15	1	1.9	1
	28-001	9	1.5	2.7	1
	32-003	36	8	1.7	6
Pearson Correlation (maximal change BP vs Anagrelide C_{max})				0.1333	
P-value				0.636	
Pearson Correlation (maximal change BP vs Log_{10} Anagrelide C_{max})				0.2042	
P-value				0.465	

BP: blood pressure
Source: Section 16.1.9.3, Annexe I, Table I, Figure 1, Figure 2

Table 5. Correlation Between BCH24426 C_{max} and Maximal Change in Diastolic Blood Pressure

Subject Group (n=12)	Subject Number	Maximal Change in Diastolic BP (mmHg)	Hour of Maximal BP Change (h)	BCH24426 C_{max} (ng/mL)	Hour of C_{max} (h)
Adolescent/Adult	03-002	34	4	8.2	2
	03-003	40	1.5	6.1	1.5
	03-007	24	6	2.8	4
	07-002	20	1	6.2	0.5
	07-004	18	2	4.9	2
	07-005	16	2	3.7	2
	10-002	12	8	10.0	1.5
	11-001	23	2	33.5	4
	21-002	20	2	6.8	1.5
Pediatric/Adolescent	14-001	20	1.5	11.2	2
	18-001	19	2	14.4	1
	20-001	15	1	8.5	1.5
Pearson Correlation (maximal change BP vs BCH24426 C_{max})				-0.0241	
P-value				0.941	
Pearson Correlation (maximal change BP vs Log_{10} BCH24426 C_{max})				-0.0546	
P-value				0.866	

BP: blood pressure
Source: Section 16.1.9.3, Annexe I, Table 2, Figure 3, Figure 4

No significant correlations between anagrelide C_{max} levels and maximal changes in diastolic pressure were found nor were for BCH24426.

Correlations in patient groups with apparent association between the exposure, C_{max} of anagrelide or BCH24426 and maximal change in heart rate were also explored. The results are shown below in (Tables 6 and 7):

Table 6. Correlation Between Anagrelide C_{max} and Maximal Change in Heart Rate

Subject Group (n=14)	Subject Number	Maximal Change in Heart Rate (bpm)	Hour of Maximal Heart Rate Change (h)	Anagrelide C_{max} (ng/mL)	Hour of C_{max} (h)
Adolescent/Adult	03-006	24	4	3.1	4
	07-001	22	1	4.9	0.5
	10-001	16	2	12.7	2
	11-001	57	1.5	25.5	1
Pediatric/Adolescent	09-001	48	12	15.5	2
	14-001	21	8	5.7	2
	15-001	28	1.5	7.4	2
	17-001	27	1.5	2.4	2
	18-001	39	2	6.1	1
	24-001	27	1.5	11.5	2
	27-001	28	12	3.3	1.5
	29-001	18	6	1.5	2
	29-002	32	6	6.0	4
	32-001	38	12	0.9	6
Pearson Correlation (maximal change heart rate vs anagrelide C_{max})				0.6266	
P-value				0.016	
Pearson Correlation (maximal change heart rate vs Log_{10} anagrelide C_{max})				0.3982	
P-value				0.158	

Source: Section 16.1.9.3, Annexe I, Table 3, Figure 5, Figure 6

Table 7. Correlation Between BCH24426 C_{max} and Maximal Change in Heart Rate

Subject Group (n=11)	Subject Number	Maximal Change in Heart Rate (bpm)	Hour of Maximal Heart Rate Change (h)	BCH24426 C_{max} (ng/mL)	Hour of C_{max} (h)
Adolescent/Adult	03-005	20	4	2.1	1.5
	07-001	22	1	3.4	2
	11-001	57	1.5	33.5	4
Pediatric/Adolescent	09-001	48	12	28.5	1
	14-001	21	8	11.2	2
	15-001	28	1.5	17.9	1.5
	17-001	27	1.5	5.8	2
	18-001	39	2	14.4	1
	24-001	27	1.5	26.2	4
	27-001	28	12	11.1	1.5
	29-002	32	6	10.2	4
Pearson Correlation (maximal change heart rate vs BCH24426 C_{max})				0.7982	
P-value				0.003	
Pearson Correlation (maximal change heart rate vs Log_{10} BCH24426 C_{max})				0.7096	
P-value				0.014	

Source: Section 16.1.9.3, Annexe I, Table 4, Figure 7, Figure 8

Both anagrelide and BCH24426 C_{max} levels were apparently correlated with maximal heart rate changes (Tables 6 and 7).

The decrease in platelet count (from pre-treatment) against anagrelide or BCH24426 daily AUC (determined on Day 30) was performed in 21 patients (n=9 in A/A patient group and n=12 in P/A patient group) who had a platelet count of ? 600 x 10^9/L. The results are shown in Table 8 below:

Table 8. Summary of Individual Platelet Count Changes from Baseline to Day 30 and AUC for Anagrelide and BCH24426

Group (n=21)	Subject Number	Change from Pre treatment Platelet Count (x 10^9/L)	Anagrelide Daily AUC (ng*h/mL)	BCH24426 Daily AUC (ng*h/mL)
Adolescent/Adult	03-001	823	26.7	53.7
(n=9 AA subjects)	07-001	240	26.6	36.8
	07-002	447	22.8	46.5
	07-003	543	23.1	59.2
	07-004	208	12.7	38.4
	07-005	247	17.9	48.3
	10-002	414	14.9	60.6
	10-003	321	7.4	23.3
	21-002	854	13.1	50.3
Pearson Correlation (P-value)			0.2046 (0.597)	0.5001 (0.170)
Pearson Correlation - Log_{10} Daily AUC (P-value)			0.2061 (0.595)	0.4782 (0.193)
Pediatric/Adolescent	09-001	1122	126.1	287.0
(n=12 PA subjects)	15-001	2271	71.1	228.9
	17-001	1662	27.4	70.0
	18-001	1353	45.6	145.1
	20-001	1029	14.3	69.2
	23-001	455	8.8	40.0
	24-001	507	30.4	118.4
	24-002	1143	40.1	179.6
	28-001	2053	14.0	78.5
	29-001	402	22.4	92.3
	29-002	1723	77.9	132.9
	32-002	564	19.6	45.4
Pearson Correlation (P-value)			0.3328 (0.291)	0.3586 (0.252)
Pearson Correlation - Log_{10} Daily AUC (P-value)			0.3975 (0.201)	0.4174 (0.177)
Combined Adolescent/Adult and Pediatric/Adolescent Data.				
Pearson Correlation (P-value)			0.4820 (0.027)	0.5770 (0.006)
Pearson Correlation - Log_{10} Daily AUC (P-value)			0.5236 (0.015)	0.6492 (0.001)

AA: Adolescent/Adult subjects; PA: Pediatric/Adolescent Subjects
Source: Section 16.1.9.3, Annexe I, Table 5, Figures 9-12b

No significant levels in correlations from the above table were found. However, when the evaluable data from patients in both groups were combined, statistically significant positive correlation was found (p=0.027). Statistically significant positive correlation was also found (p<0.01) for the AUC values of BCH24426 and platelet counts.

The starting dose and final dose are summarized below in Table 9 below:

Table 9. Starting Dose and Final Dose of All Patients

Subject Group	Subject Number	Total Daily Starting Dose (mg)	Total Daily Final Dose (mg)	Change from Starting Dose (mg)	Final Dosing Regimen
Pediatric/Adolescent	09-001	1.0	6.0	5.0	3mg bid
	14-001	1.0	2.5	1.5	1mg qd 0.5mg qd 1mg qd
	14-002	1.0	1.0	0	0.5mg bid
	15-001	1.0	4.5	3.5	1.5mg tid
	17-001	1.5	1.0	-0.5	0.5mg bid
	18-001	1.0	4.0	3.0	1mg qid
	20-001	1.0	1.0	0	0.5mg bid
	23-001	1.0	1.0	0	0.5mg bid
	24-001	0.5*	1.5	1.0	1.5mg qd
	24-002	1.0	3.0	2.0	1mg tid
	27-001	1.5	3.0	1.5	1mg tid
	28-001	1.0	2.0	1.0	1mg bid
	29-001	1.0	2.0	1.0	0.5mg qid
	29-002	0.75	4.5	3.75	1.5mg tid
	32-001	1.5	1.0	-0.5	0.5mg bid
	32-002	1.0	1.0	0	0.5mg bid
	32-003	1.0	1.0	0	0.5mg bid
Adolescent/Adult	03-001	2.0	2.0	0	1mg bid
	03-002	1.0	3.0	2.0	1.5mg bid
	03-003	1.0	2.0	1.0	0.5mg qid
	03-005	1.5	2.0	0.5	0.5mg qid
	03-006	1.5	3.5	2.0	2mg qd 1.5mg qd
	03-007	0.5*	0.5	0	0.5mg qd
	07-001	1.0	1.0	0	0.5mg bid
	07-002	0.5	1.5	1.0	0.5mg tid
	07-003	1.5	1.0	-0.5	1mg qd
	07-004	0.5*	1.0	0.5	0.5mg bid
	07-005	0.5*	1.5	1.0	0.5mg tid
	07-006	0.5*	0.5	0	0.5mg qd
	10-001	1.0	2.0	1.0	1mg bid
	10-002	1.0	2.0	1.0	1mg bid
	10-003	1.5	0.5	-1.0	0.5mg qd
	10-004	0.5*	0.5	0	0.5mg qd
	11-001#	1.0	7.0	6.0	4mg qd 3mg qd
	21-002	0.5	1.0	0.5	0.5mg bid
Pediatric	Median	1.0	1.25	0.5	na
	Mean	1.0	2.1	1.1	
	SD	0.3	1.5	1.6	
Adolescent	Median	1.0	2.0	1.0	na
	Mean	1.0	2.6	1.5	
	SD	0.2	1.7	1.8	
Adolescent/Adult	Median	1.0	1.5	0.5	na
	Mean	1.0	1.8	0.8	
	SD	0.4	1.6	1.5	

* Subjects naïve at study entry commenced anagrelide therapy at 0.5mg qd per protocol.
# This subject received single doses in excess of the recommended 2.5mg.
na=not applicable
Pediatric (≤11 years old); adolescent (12-15 years old); adolescent/adult (≥16 years old)
Source: Section 16.3, Listing 1.1, Listing 7.3, and Listing 7.4

There does not appear to be any differences in dose adjustments (mean changes from starting dose to final dose) between patient age group (1.1 mg for pediatric group, 1.5 mg for adolescent group, and 0.8 mg for adult group).

Overall, sponsor recommends adult dosing administration guidelines to pediatrics as well and this appears reasonable.

C. Intrinsic Factors:

Linear regression of the PK dataset for anagrelide or BCH24426 against age revealed a significant positive correlation for anagrelide, but not for BCH24426. However, the slope (R^2 = 0.19) was relatively shallow.

D. Extrinsic Factors: Not Analyzed

E. General Biopharmaceutics

The currently approved Agrylin 0.5 and 1 mg capsules were used.

F. Analytical Section:

An analytical method using solid phase extraction followed by LC/MS/MS assay (b) (4) for the quantitation of anagrelide and metabolites. The method was found to be adequately validated.

Anagrelide:

Standard Curve: (n=8)
0.05, 0.1, 0.5, 2.0, 10.0, 15.0, 18.0, and 20.0 ng/mL
Recovery(%):
95.4 (n=6), 98.6 (n=3), 105.4 (n=5), 103.5 (n=6), 97.3 (n=6), 96 (n=6), 98.9 (n=6), and 103.5% (n=6), respectively
Precision (CV%):
7.3 (n=6), 12.9 (n=6), 9.6 (n=5), 5.3 (n=6), 6.9 (n=6), 9.0 (n=6), 10.6 (n=6), and 3.5% (n=6), respectively

QC: (n=4)
0.15, 8.0, 17.5, and 35.0 ng/mL
Recovery(%):
104.0 (n=12), 108.3 (n=12), 100.0 (n=12), and 99.1% (n=2), respectively
Precision (CV%):
11.8 (n=12), 11.3 (n=12), 9.7 (n=12), and 6.7% (n=2), respectively

BCH24426:

Standard Curve: (n=8)
0.1, 0.2, 0.5, 1.0, 4.0, 20.0, 30.0, 36.0, and 40.0 ng/mL
Recovery(%):
97.7 (n=6), 94.5 (n=6), 108 (n=5), 103.5 (n=5), 97.5 (n=5), 100.0 (n=6), 96.7 (n=5), and 103.3% (n=6), respectively
Precision (CV%):
12.0 (n=6), 14.2 (n=6), 15.4 (n=5), 11.0 (n=5), 8.6 (n=5), 11.9 (n=6), 5.1 (n=5), and 3.3% (n=6), respectively

QC: (n=4)
0.3, 16.0, 35.0, and 70.0 ng/mL
Recovery(%):
114.3 (n=12), 106.3 (n=12), 100.3 (n=12), and 96.7% (n=2), respectively
Precision (CV%):
17.3 (n=12), 13.5 (n=12), 14.5 (n=12), and 1.5% (n=2), respectively

RL603:

Standard Curve: (n=8)
0.05, 0.1, 0.5, 2.0, 10.0, 15.0, 18.0, and 20.0 ng/mL
Recovery(%):
110.2 (n=2), 96.1 (n=5), 101.8 (n=6), 101.5 (n=5), 98.9 (n=6), 90.7 (n=6), 98.3 (n=3), and 108.5% (n=6), respectively
Precision (CV%):
3.0 (n=2), 10.5 (n=5), 8.6 (n=6), 6.5 (n=5), 7.4 (n=6), 6.7 (n=6), 11.8 (n=3), and 5.0% (n=6), respectively

QC: (n=4)
0.15, 8.0, 17.5, and 35.0 ng/mL
Recovery(%):
97.3 (n=12), 108.0 (n=12), 101.1 (n=12), and 92.9% (n=2), respectively
Precision (CV%):
17.3 (n=12), 10.6 (n=12), 13.1 (n=12), and 7.6% (n=2), respectively

V. Labeling Recommendations

The proposed package insert is attached in Appendix 1. Although this package insert contains other changes related to drug-drug interactions, these will be addressed in a separate review as data pertaining to this was administratively changed to supplement SLR-009 (with the same submission date of 03/12/04). Clinical Pharmacology related changes (blue underlined for addition; red with double strikethrough for deletion) regarding pediatrics are shown below.

1. Under Clinical Pharmacology Section (P.15)

Pharmacokinetic (PK) data from fasting pediatric (age range 7-14 years) and adult (age range 16-86 years) patients with thrombocythemia secondary to a myeloproliferative disorder (MPD), indicate that dose- and body weight-normalized exposure, C_{max} and AUC_t, of anagrelide were lower in the pediatric patients compared to the adult patients (C_{max} 48%, AUC_t 55%) (b) (4)

(b) (4)

2. Under Pediatric Clinical Studies Subsection of Clinical Trials Section (p.17):

(b) (4)

VI. Appendices

1. Proposed Package Insert (Original and Annotated)

2. Study Synopsis for SPD422-202

NDA 20-333 (SE5-008) for Agrylin (Anagrelide HCl) 0.5 and 1.0 mg Capsules

Appendix 1

Sponsor's Proposed Labeling (03/12/04 Version)

9 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

NDA 20-333 (SE5-008) for Agrylin (Anagrelide HCl) 0.5 and 1.0 mg Capsules

Appendix 2

Study Synopsis for Pediatric Study SPD422-202

SYNOPSIS

Title of Study:	An Open Label, Single-Arm, MultiCenter, Safety, Pharmacokinetic and Pharmacodynamic, Phase II Study of Anagrelide Hydrochloride in Paediatric and Adult Subjects with Thrombocythemia Secondary to Myeloproliferative Disorders.
Pharmacokinetic Objectives:	To assess the steady state pharmacokinetic profile of anagrelide in paediatric/adolescent (≤15 years old) subjects and compare with the steady state pharmacokinetic profile of anagrelide in adolescent/adult (>16 years old) subjects with thrombocythemia secondary to a myeloproliferative disorder (MPD).
Pharmacodynamic Objectives:	To evaluate the correlation, if any, between anagrelide daily dose, resultant anagrelide plasma concentrations and platelet count in paediatric/adolescent (≤15 year old) subjects and adolescent/adult (>16 year old) subjects with thrombocythemia secondary to a myeloproliferative disorder (MPD).
Study Design:	A Phase II, open label, single arm, multi-center, (prospective) pharmacokinetic and retrospective study utilizing pediatric/adolescent (≤15 years old) and adolescent/adult (>16 years old) subjects with thrombocythemia secondary to myeloproliferative disorders who were either currently on anagrelide treatment (anagrelide experienced) or were anagrelide treatment naïve. Subjects on a stable maintenance regimen of anagrelide prior to study entry were dosed in accordance with their previously prescribed anagrelide daily dose and regimen. Subjects undergoing anagrelide titration at study entry continued titration, upward or downward, on a weekly basis. Subjects who were anagrelide naïve commenced daily dosing (Day 1) at 0.5mg QD, and titration was allowed on a weekly basis. The maximum positive increment was limited to 0.5mg/day. Pharmacokinetic sampling was conducted on all subjects at Day 30 to determine the pharmacokinetic profile of anagrelide and its metabolites (RL603 and BCH24426) during one dosing interval period. Blood samples were collected at pre-dose (0-hour), 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours, unless the dosing interval was shorter in length. In that event, the last blood sample drawn corresponded to the length of the dosing interval (i.e. if dosing interval was 6 hours, the last blood drawn was collected at 6

	hours: the 8- and 12-hour blood draws were not collected).
Pharmacokinetic Results and Conclusions:	Due to the nature of this trial, the dosage regimen varied between subjects. A dosage regimen of 0.5mg BID was the more commonly utilized regimen at day 30, and this was the only sub-group with a sufficient number of subjects to provide meaningful comparisons between pediatric/adolescent (PA; n=6) and adolescent/adult (AA; n=4) subjects. In subjects treated with 0.5mg BID the day 30 mean maximum plasma concentration of anagrelide in PA subjects was 63% of that in AA subjects (PA 1.9ng/mL, AA 3.1 ng/mL), although the difference was not statistically significant. The mean areas under the curve for the dose interval were similar in this dosing sub-group (PA 8.2ng*h/mL, AA 8.6ng*h/mL). The mean maximum plasma concentration of the major pharmacologically active metabolite BCH24426 for the PA and AA subjects was nearly 3 times higher than for anagrelide, but there were no significant differences between the groups in any pharmacokinetic parameter. The mean maximum plasma concentration of the pharmacologically inactive metabolite RL603 in PA subjects on 0.5mg BID was some 21% that of anagrelide. Concentrations in PA subjects were only ~30% of those in the AA group (p=0.019). Normalisation by dose and bodyweight to70kg and assessment of data across all subjects (PA, n=16; AA, n=18) irrespective of dosing frequency confirmed the findings provided by the 0.5mg BID results. Exposure to anagrelide was significantly lower in PA subjects than AA subjects (Cmax 48%, AUCτ 55%), but there were no significant differences for BCH24426. Exposure to RL603 was confirmed to be significantly less for PA subjects than for AA subjects. A significant correlation of exposure in terms of Cmax and AUCτ with age was established by linear regression. However, the slope was very shallow, indicating that age, although a contributory factor, numerically was of little importance. A linear relationship of exposure to dose was established for anagrelide, BCH24426 and RL603 over the dose range 0.5-1.5mg by considering all the available data, irrespective of

	subject group, bodyweight or dosing frequency. It was concluded that exposure to anagrelide and the inactive metabolite RL603 was significantly lower in pediatrics, adolescents when dose and bodyweight differences were taken into account, but that there was no difference in exposure to the major active metabolite BCH24426.
Pharmacodynamic Results and Conclusions:	Significant positive correlations were identified between maximal increases in pulse rate and corresponding maximum plasma concentrations of anagrelide and BCH24426 (especially BCH24426). In addition, decreases in platelet count were significantly correlated with anagrelide and BCH24426 plasma exposure when the data from both age groups were combined; however, these relationships were no longer statistically significant when the data were analyzed by age group

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/s/

Tien-Mien Chen
7/14/04 03:54:54 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/14/04 04:20:17 PM
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