QUESTIONS FOR THE
ONCOLOGY DRUGS ADVISORY COMMITTEE
SEPTEMBER 14, 2005 MEETING

NDA 21877 Arranon (Nelarabine)

APPLICANT GlaxoSmithKline

PROPOSED INDICATION Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

The principal support for this NDA comes from two Phase 2 non-comparative clinical trials, one in children and one in adults.

Pediatric Study (PGAA2001)

The pediatric study (PGAA2001) was conducted by the Children's Oncology Group in patients with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Seventy (70) patients were treated with 650 mg/m^2/day of nelarabine administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days; 39 of whom had received two or more prior induction regimens, and 31 of whom had received one prior induction regimen.

Two or more prior inductions is the Sponsor's proposed indication.

Table 1: Response Rates by Number of Prior Inductions

Number (%) of Subjects		
Response	**1 Prior Induction N=31**	**≥ 2 Prior Inductions N=39**
CR (%) 95% CI	13 (42) 25, 61	5 (13) 4, 27
CR+CR*	15 (48%) 30, 67	9 (23) 11, 39
CR* = CR with incomplete hematologic recovery (hemoglobin, ANC, platelets)		

Table 2: Remission duration of non-transplanted patients

1 Prior Induction	≥ 2 Prior Inductions
Remission duration (weeks)	Remission duration (weeks)
33.1 (sys)*	42.1 (IT + sys)*
9.1 (IT)*	9.3
6.3	6.1
2.3	3.6
1.4+	3.3

* Patients had other systemic (sys) and/or intrathecal (IT) therapy after nelarabine, but before progression.

Adult Study (CALGB) (PGAA 2002)

The CALGB adult study included 39 treated patients, 26 of whom had T-ALL and 13 of whom had T-LBL. Twenty-eight patients had relapsed following or were refractory to at least two prior induction regimens. This is the Applicant's proposed indication. Nelarabine 1,500 mg/m^2 was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days.

Table 3: Response Rates by Number of Prior Inductions

	1 Prior Induction (N=11)	≥2 Prior Inductions (N=28)	Total (N=39)
Complete Response (CR)	2 (18) [2, 52]	5 (18) [6, 37]	7 (18) [8, 34]
CR + CR*	3 (27) [6, 61]	6 (21) [8, 41]	]9 (23) [11, 39]

* either failure of hematologic recovery (1 patient) or short duration response (1 patient)

Table 4: Remission duration of non-transplanted patients

Remission duration (weeks)	
1 Prior Induction Regimen	≥2 Prior Induction Regimens
217	195+
5	30
	15
	19
	4

Table 5 Neurologic Adverse Events in Pediatric Patients Treated with 650 mg/m^2 of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days

Nervous System Disorders	Percentage of Patients; N = 84					
Preferred (Category) Term Subterm	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Headache	**0**	**8**	**2**	**4**	**2**	**17**
Peripheral Neurologic Disorders	**0**	**1**	**4**	**7**	**0**	**12**
Neuropathy, peripheral	0	0	4	2	0	6
Peripheral sensory neuropathy	0	0	0	6	0	6
Peripheral motor neuropathy	0	1	0	2	0	4
Lowered Consciousness	**0**	**1**	**4**	**1**	**1**	**7**
Somnolence	0	1	4	1	1	7
Peripheral Neurologic Disorders	**0**	**1**	**4**	**7**	**0**	**12**
Fatigue	0	0	1	0	0	1
Lethargy	0	1	0	0	0	1
Hypoesthesia	**0**	**1**	**1**	**4**	**0**	**6**
Seizures	**0**	**0**	**0**	**0**	**6**	**6**
Convulsion	0	0	0	0	4	4
Grand mal convulsion	0	0	0	0	1	1
Status epilepticus	0	0	0	0	1	1
Motor dysfunction	**0**	**1**	**1**	**1**	**0**	**4**
Nervous system disorder	**0**	**1**	**2**	**0**	**0**	**4**
Paresthesia	**0**	**0**	**2**	**1**	**0**	**4**
Tremor	**0**	**1**	**2**	**0**	**0**	**4**
Ataxia	**0**	**1**	**0**	**1**	**0**	**2**

Table 6 Neurologic Adverse Events in Adult Patients Treated with 1,500 mg/m^2 of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days

Nervous System Disorders System Organ Class Preferred (Category) Term Subterm	Percentage of Patients; N =103					
	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Lowered Consciousness	**0**	**33**	**17**	**11**	**3**	**63**
Fatigue	0	23	15	10	2	50
Somnolence	0	20	3	0	0	23
Depressed level of consciousness	0	4	1	0	1	6
Coma	0	0	0	0	1	1
Lethargy	0	0	1	0	0	1
Loss of consciousness	0	0	0	1	0	1
Dizziness	**0**	**14**	**8**	**0**	**0**	**21**
Peripheral Neurologic Disorders	**0**	**8**	**9**	**2**	**0**	**18**
Peripheral sensory neuropathy	0	7	6	0	0	13
Peripheral motor neuropathy	0	3	3	1	0	7
Neuropathy, peripheral	0	2	2	1	0	5
Hypoesthesia	**1**	**5**	**10**	**2**	**0**	**17**
Headache	**0**	**11**	**3**	**1**	**0**	**15**
Paresthesia	**0**	**11**	**4**	**0**	**0**	**15**
Ataxia	**0**	**1**	**6**	**2**	**0**	**9**
Tremor	**0**	**2**	**3**	**0**	**0**	**5**
Neuropathy	**0**	**0**	**4**	**0**	**0**	**4**
Amnesia	**0**	**2**	**1**	**0**	**0**	**3**
Dysguesia	**0**	**2**	**1**	**0**	**0**	**3**
Balance disorder	**0**	**1**	**1**	**0**	**0**	**2**
Sensory loss	**0**	**0**	**2**	**0**	**0**	**2**
Seizures	**0**	**0**	**0**	**1**	**0**	**1**
Convulsion	0	0	0	1	0	1

Grade 4+ = Grade 4 and Grade 5

QUESTIONS FOR THE COMMITTEE

In the two relatively small non comparative clinical trials only CR and CR* can be interpreted. Time to event endpoints such as survival can not be interpreted without a randomized trial. CR and CR* duration is confounded in many of the cases because patients were transplanted or received other systemic chemotherapy prior to disease progression. The relative value of CR and CR* is also an issue.

1. In pediatric patients with ≥ 2 prior inductions 9 of 39 (23%) of patients had CR or CR*. Four of 9 CR or CR* patients who did not have their CR or CR* duration confounded by subsequent Transplant or other Systemic chemotherapy had CR or CR* durations of 3.3, 3.6, 6.1 and 9.3 weeks.

   Are these results reasonably likely to predict clinical benefit in this setting?

2. In adult patients with ≥ 2 prior inductions 6 of 28 (21%) of patients had CR or CR*. Five of 6 CR or CR* patients who did not have their CR or CR* duration confounded by subsequent Transplant or other Systemic chemotherapy had CR or CR* durations of 4, 15, 19, 30 and 195 +weeks.

   Are these results reasonably likely to predict clinical benefit in this setting?

3. Is the benefit/risk ratio favorable?

4. Should this NDA be granted accelerated approval?