ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 02/12/2015

A Study of MabThera (Rituximab) Plus Chlorambucil in Patients With Previously Untreated Chronic Lymphocytic Leukemia.

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00738374

Purpose

This single arm study will assess the efficacy and safety of MabThera + chlorambucil as induction therapy, followed in responders by maintenance therapy or observation in elderly patients with previously untreated chronic lymphocytic leukemia. During the induction phase patients will receive 2 x 4 weekly courses of chlorambucil followed by 8 x 4 weekly courses of chlorambucil + MabThera. Subsequently, responders will be randomized to receive 12 doses of MabThera given every 8 weeks, or no further treatment. The anticipated time on study treatment is 2+ years, and the target sample size is <100 individuals.

Condition	Intervention	Phase
Lymphocytic Leukemia, Chronic	Drug: rituximab [MabThera/Rituxan] Drug: chlorambucil	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Safety/Efficacy Study
Official Title: A Study of Chlorambucil Plus MabThera as Induction Therapy Followed in Responders by Maintenance Therapy Versus Observation on Response Rate in Patients >=60 Years With Previously Untreated Chronic Lymphocytic Leukemia

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Percentage of Participants With Documented CR, CRi, or PR at the End of Induction Treatment [Time Frame: Month 10] [Designated as safety issue: No]

CR defined as: 1) laboratory CR: peripheral blood lymphocytes (PBL) less than (<) 4000/microliter (µL), neutrophils (PMN) greater than (>) 1500/µL, platelets >100,000/µL, and hemoglobin (Hb) >11 grams per deciliter (g/dL); 2) clinical CR: lymph nodes (LN) <1.5 centimeter (cm), and no constitutional symptoms, hepatomegaly (HM) or splenomegaly (SM); 3) instrumental CR: LN <1.5 cm and no HM/SM, and 4) bone marrow (BM) CR: normocellular aspirate/biopsy for participant age <30 percent (%) lymphocytes, and no B cell lymphoid nodules. CRi was defined as CR with anemia, thrombocytopenia, or neutropenia not related to chronic lymphocytic leukemia (CLL), with no clonal infiltrate in aspirate or biopsy. PR defined as: a 50% decrease in PBL, a 50% decrease in LN size, no increase in LN size, no new enlarged LN, a 50% reduction from baseline (BL) in the HM/SM, and 1 of the following: PMN >1500/µL, platelets >100,000/µL or >50% improvement from BL, and Hb >11.0 g/dL or >50% improvement from BL.

Secondary Outcome Measures:

- Percentage of Participants With Documented CR, CRi, or PR at the End of Study [Time Frame: Month 35] [Designated as safety issue: No]
  CR defined as: 1) laboratory CR: PBL <4000/µL, PMN > 1500/µL, platelets > 100,000/µL, and Hb > 11 g/dL; 2) clinical CR: LN < 1.5 cm, and no constitutional symptoms, HM or SM; 3) instrumental CR: LN < 1.5 cm and no HM/SM, and 4) bone marrow CR: normocellular aspirate/biopsy for participant age < 30% lymphocytes, and no B cell lymphoid nodules. CRi was defined as CR with anemia, thrombocytopenia, or neutropenia not related to CLL, with no clonal infiltrate in aspirate or biopsy. PR defined as: a 50% decrease in PBL, a 50% decrease in LN size, no increase in LN size, no new enlarged LN, a 50% reduction from BL in the HM/SM, and 1 of the following: PMN > 1500/µL, platelets > 100,000/µL or > 50% improvement from BL, and Hb >11.0 g/dL or > 50% improvement from BL.
- Percentage of Participants With CR, CRi, PR, Stable Disease (SD), Progressive Disease (PD), Relapse, or Nodular PR at the End of Induction Treatment [Time Frame: Month 10] [Designated as safety issue: No]
  CR, CRi, and PR as previously defined. PD was defined by 1 of the following: 1) lymphadenopathy: any new lesion, HM/SM, or other organ infiltrates, or a greater than or equal to (≥) 50% increase in greatest diameter of any previously noted lesion; 2) a ≥ 50% increase in previously noted HM/SM, or new appearance of HM/SM; 3) a ≥ 50% increase in blood lymphocyte count with at least 5000 B lymphocytes/µL; 4) transformation to a more aggressive histology, e.g., Richter's syndrome; or 5) occurrence of cytopenia attributable to CLL. SD was defined by the absence of necessary criteria to achieve CR or PR, but no advancement to PD. Relapse was defined by a previously noted CR or PR with advancement to PD after a period of ≥ 6 months. Nodular PR was defined by the presence of residual lymphoid nodules.
- Percentage of Participants With CR, PR, SD, PD, Relapse, or Nodular PR at the End of Study [Time Frame: Month 35] [Designated as safety issue: No]
  CR, and PR as previously defined. PD was defined by 1 of the following: 1) lymphadenopathy: any new lesion, HM/SM, or other organ infiltrates, or a ≥ 50% increase in greatest diameter of any previously noted lesion; 2) a ≥50% increase in previously noted HM/SM, or new appearance of HM/SM; 3) a ≥50% increase in blood lymphocyte count with at least 5000 B lymphocytes/µL; 4) transformation to a more aggressive histology, e.g., Richter's syndrome; or 5) occurrence of cytopenia attributable to CLL. SD was defined by the absence of necessary criteria to achieve CR or PR, but no advancement to PD. Relapse was defined by a previously noted CR or PR with advancement to PD after a period of ≥6 months. Nodular PR was defined by the presence of residual lymphoid nodules.
- Number of Participants With Immunophenotypic CR - BM, Immunophenotypic CR - Peripheral Blood (PB), Molecular CR - BM, or Molecular CR - PB at the End of Induction Treatment [Time Frame: Month 10] [Designated as safety issue: No]
  Immunophenotypic CR was defined as the absence of minimal residual disease (MRD) evaluated in participants with CR by 4-color flow cytometry of PB and BM B cells to confirm that tissue was comprised of non-CLL cells. Molecular CR was defined as the absence of MRD evaluated in participants with CR by quantitative polymerase chain reaction (PCR) in PB and BM B cells to confirm that tissue was comprised of non-CLL cells.
- Percentage of Participants With CR, CRi, PR, SD, PD, or Relapse at the End of Study [Time Frame: Month 35] [Designated as safety issue: No]
  CR, CRi, PR, SD, PD, relapse, and nodular PR as previously defined.
- Percentage of Participants With Immunophenotypic CR - BM or Immunophenotypic CR - PB at the End of Study [Time Frame: Month 35] [Designated as safety issue: No]
  Immunophenotypic CR was defined as the absence of MRD evaluated in participants who achieved CR by 4-color flow cytometry of PB and BM B cells to confirm that tissue was comprised of non-CLL cells.
- Percentage of Participants With Molecular CR - BM or Molecular CR - PB at the End of Study [Time Frame: Month 35] [Designated as safety issue: No]
  Molecular CR was defined as the absence of MRD evaluated in participants who achieved CR by quantitative PCR in PB and BM B cells to confirm that tissue was comprised of non-CLL cells.

- Number of Participants With Disease Progression, Relapse, Death, Withdrawal Because of an Adverse Event (AE), or New CLL Treatment [Time Frame: Screening, Days 1 and 15 of Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  Event-free Survival (EFS) was defined as the time from the first dose of study treatment to the date of first documentation of disease progression, relapse for participants with previous CR, death due to any cause, withdrawal due to AE, or beginning new CLL treatment. CR and PD as previously defined. Participants were censored at the time of data cut-off to the most recent date of disease assessment. Participants without a post-BL disease assessment were censored at the time of first dose of study treatment.
- EFS [Time Frame: Screening, Days 1 and 15 of Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  The median time, in days, from the the date of first dose of study treatment to the date of first documentation of disease progression, relapse for participants with CR, death due to any cause, withdrawal due to AE, or new CLL treatment. CR and PD as previously defined. Participants were censored at the time of data cut-off to the most recent date of disease assessment. Participants without a post-BL disease assessment were censored at the time of first dose if study treatment. The 95% CI was determined using Kaplan-Meier methodology.
- Number of Participants With Disease Progression or Death [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  Progression-free survival (PFS) was defined as the time from the first dose of study treatment to the first documentation of disease progression or death. PD as previously defined. Participants who were withdrawn from the study without documented disease progression were censored at the date of the last tumor assessment when the participant was known to be progression-free. Participants without a post-BL tumor assessment, but known to be alive, were censored at the time of the first dose of study treatment.
- PFS [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  The median time, in days, from the date of the first dose of study treatment to the date of first documentation of disease progression or death. CR and PD as previously defined. Participants who were withdrawn from the study without documented disease progression were censored at the date of the last tumor assessment when the participant was known to be progression-free. Participants without a post-BL tumor assessment, but known to be alive, were censored at the time of the first dose of study treatment. The 95% CI was determined using Kaplan-Meier methodology.
- Number of Participants With New CLL Treatment or Death [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  Time to new CLL treatment (TTNT) was defined as the time from the first dose of study treatment to the date of new CLL treatment received or the date of death from any cause. Participants who did not receive new CLL treatment and were alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment.
- Time to Next Treatment (TTNT) [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  The mean time, in days, from the date of the first dose of study treatment to the date of new CLL treatment or the date of death from any cause. Participants who did not receive new CLL treatment and were alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment. Mean survival time and it's standard error (SE) were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
- Number of Participants Who Died [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

  Overall Survival (OS) was defined as the time from the date of the first dose of study treatment to the date of death due to any cause. Participants were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment.
- OS [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]

The mean time, in days, from the date of the first dose of study treatment to the date of death due to any cause. Participants were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment. The mean survival time and it's SE were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

- Number of Participants With PD or Death After a Confirmed CR, CRi, or PR [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]
  Duration of response was defined as the time from the date of the first documented CR, CRi, or PR to the date of disease progression or death. CR, CRi, PR, and PD as previously defined. Participants with no documented PD after CR, CRi, or PR were censored at the last date at which they were known to have had CR, CRi, or PR, respectively.
- Duration of Response [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]
  The mean time, in days, from the date of first documented CR, CRi or PR to the date disease progression or death. CR, CRi, PR, and PD as previously defined. Participants with no documented PD after CR, CRi, or PR were censored at the last date at which they were known to have had CR, CRi, or PR, respectively.
- Number of Participants With PD or Death After a Confirmed CR/CRi [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]
  Disease-free survival was defined at the time from the date of first documented CR or CRi to the date of disease progression or death. CR, CRi, and PD as previously defined. Participants with no documented PD after CR or CRi were censored on the last date at which they were known to have had CR or CRi.
- Disease-Free Survival [Time Frame: Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.] [Designated as safety issue: No]
  The mean time, in days, from the date of first documented CR or CRi to the date of disease progression or death. CR, CRi, and PD as previously defined. Participants with no documented PD after CR or CRi were censored on the last date at which they were known to have had CR or CRi. In both groups, the mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Enrollment: 97
Study Start Date: November 2008
Primary Completion Date: January 2013
Study Completion Date: January 2013

Arms	Assigned Interventions
Experimental: 1	Drug: rituximab [MabThera/Rituxan] 375mg/m2 iv on day 1 of course 3; 500mg/m2 iv on day 1 of courses 4-8 (induction phase); 375mg/m2 iv every 8 weeks (maintenance phase). Drug: chlorambucil 8mg/m2 po on days 1-7 of courses 1-8

Eligibility

Ages Eligible for Study: 60 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- adult patients, >=60 years of age;
- CD20+ chronic lymphocytic leukemia (CLL);
- no previous treatment for CLL;
- ECOG performance status 0-1.

Exclusion Criteria:

- co-morbid conditions requiring long term use of systemic corticosteroids during study treatment;
- history of severe cardiac disease;
- transformation to aggressive B-cell malignancy.

Contacts and Locations

Locations

Italy

Catanzaro, Calabria, Italy, 88100
Cosenza, Calabria, Italy, 87100
Reggio Calabria, Calabria, Italy, 89100
Napoli, Campania, Italy, 80131
Bologna, Emilia-Romagna, Italy, 40138
Ferrara, Emilia-Romagna, Italy, 44100
Roma, Lazio, Italy, 00161
Roma, Lazio, Italy, 00144
Genova, Liguria, Italy, 16132
Milano, Lombardia, Italy, 20162
Milano, Lombardia, Italy, 20122
Torino, Piemonte, Italy, 10126
Torino, Piemonte, Italy, 10126
Bari, Puglia, Italy, 70124
Catania, Sicilia, Italy, 95124
Messina, Sicilia, Italy, 98165
Firenze, Toscana, Italy, 50135
Siena, Toscana, Italy, 53100
Padova, Veneto, Italy, 35128
Verona, Veneto, Italy, 37134

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Study Results

Participant Flow

Reporting Groups

	Description
Chlorambucil (CLB) Plus (+) Rituximab (R): Induction Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 milligrams per square meter (mg/m^2), orally (PO) as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, intravenously (IV), on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with complete response (CR), complete response with incomplete bone marrow recovery (CRi), or partial response (PR) were randomized to receive either rituximab, 375 mg/m^2, IV, every 8 weeks for up to 24 months, or to be observed for up to 24 months with no further treatment.
CLB + R: Completed Induction Treament But Not Randomized	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants were not randomized to receive further treatment or observation.
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Induction Treatment Phase

	Chlorambucil (CLB) Plus (+) Rituximab (R): Induction Treatment	CLB + R: Completed Induction Treament But Not Randomized	CLB + R: Maintenance Treatment	CLB + R: Observation
Started	97	0	0 [1]	0 [1]
Completed	73	0	0	0
Not Completed	24	0	0	0
Adverse Event	14	0	0	0
Disease progression/relapse/stable	4	0	0	0
Physician Decision	2	0	0	0
Protocol Violation	2	0	0	0
Non-compliance	1	0	0	0
Withdrawal by Subject	1	0	0	0

[1] Participants were randomized at the end of the Induction Treatment Phase.

Maintenance Treatment/Observation Phase

	Chlorambucil (CLB) Plus (+) Rituximab (R): Induction Treatment	CLB + R: Completed Induction Treament But Not Randomized	CLB + R: Maintenance Treatment	CLB + R: Observation
Started	0 [1]	7	34	32
Completed	0	0	27	20
Not Completed	0	7	7	12
Adverse Event	0	1	2	0
Disease progression/relapse/stable	0	4	5	11
Withdrawal by Subject	0	0	0	1
Protocol Violation	0	1	0	0
Not Specified	0	1	0	0

[1] Participants were randomized to either maintenance therapy or observation at the end of induction.

Baseline Characteristics

Analysis Population Description
All enrolled participants.

Reporting Groups

	Description
CLB + R: Not Randomized	Participants began a 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants who completed the induction treatment with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, every 8 weeks for up to 24 months, or to be observed for up to 24 months with no further treatment.
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Baseline Measures

	CLB + R: Not Randomized	CLB + R: Maintenance Treatment	CLB + R: Observation	Total
Number of Participants	31	34	32	97
Age, Continuous [units: years] Mean (Standard Deviation)	74.7 (6.5)	69.8 (5.4)	70.2 (5.1)	71.7 (6.1)
Gender, Male/Female [units: participants]				
Female	13	10	9	32
Male	18	24	23	65

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Documented CR, CRi, or PR at the End of Induction Treatment
Measure Description	CR defined as: 1) laboratory CR: peripheral blood lymphocytes (PBL) less than (<) 4000/microliter (µL), neutrophils (PMN) greater than (>) 1500/µL, platelets >100,000/µL, and hemoglobin (Hb) >11 grams per deciliter (g/dL); 2) clinical CR: lymph nodes (LN) <1.5 centimeter (cm), and no constitutional symptoms, hepatomegaly (HM) or splenomegaly (SM); 3) instrumental CR: LN <1.5 cm and no HM/SM, and 4) bone marrow (BM) CR: normocellular aspirate/biopsy for participant age <30 percent (%) lymphocytes, and no B cell lymphoid nodules. CRi was defined as CR with anemia, thrombocytopenia, or neutropenia not related to chronic lymphocytic leukemia (CLL), with no clonal infiltrate in aspirate or biopsy. PR defined as: a 50% decrease in PBL, a 50% decrease in LN size, no increase in LN size, no new enlarged LN, a 50% reduction from baseline (BL) in the HM/SM, and 1 of the following: PMN >1500/µL, platelets >100,000/µL or >50% improvement from BL, and Hb >11.0 g/dL or >50% improvement from BL.
Time Frame	Month 10
Safety Issue?	No

Analysis Population Description

Intent to treat (ITT) population: all consented participants who received at least 1 dose of rituximab.

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Percentage of Participants With Documented CR, CRi, or PR at the End of Induction Treatment [units: percentage of participants] Number (95% Confidence Interval)	82.4 (74.25 to 90.46)

Statistical Analysis 1 for Percentage of Participants With Documented CR, CRi, or PR at the End of Induction Treatment

Statistical Analysis Overview	Comparison Groups	CLB + R: All Participants
	Comments	Analysis compared responders and non-responders.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0008
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Documented CR, CRi, or PR at the End of Study
Measure Description	CR defined as: 1) laboratory CR: PBL <4000/µL, PMN > 1500/µL, platelets > 100,000/µL, and Hb > 11 g/dL; 2) clinical CR: LN < 1.5 cm, and no constitutional symptoms, HM or SM; 3) instrumental CR: LN < 1.5 cm and no HM/SM, and 4) bone marrow CR: normocellular aspirate/biopsy for participant age < 30% lymphocytes, and no B cell lymphoid nodules. CRi was defined as CR with anemia, thrombocytopenia, or neutropenia not related to CLL, with no clonal infiltrate in aspirate or biopsy. PR defined as: a 50% decrease in PBL, a 50% decrease in LN size, no increase in LN size, no new enlarged LN, a 50% reduction from BL in the HM/SM, and 1 of the following: PMN > 1500/µL, platelets > 100,000/µL or > 50% improvement from BL, and Hb >11.0 g/dL or > 50% improvement from BL.
Time Frame	Month 35
Safety Issue?	No

Analysis Population Description

All randomized participants.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.

	Description
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	34	32
Percentage of Participants With Documented CR, CRi, or PR at the End of Study [units: percentage of participants] Number (95% Confidence Interval)	55.9 (39.19 to 72.57)	34.4 (17.92 to 50.83)

Statistical Analysis 1 for Percentage of Participants With Documented CR, CRi, or PR at the End of Study

Statistical Analysis Overview	Comparison Groups	CLB + R: Maintenance Treatment, CLB + R: Observation
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0795
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants With CR, CRi, PR, Stable Disease (SD), Progressive Disease (PD), Relapse, or Nodular PR at the End of Induction Treatment

Measure Description	CR, CRi, and PR as previously defined. PD was defined by 1 of the following: 1) lymphadenopathy: any new lesion, HM/SM, or other organ infiltrates, or a greater than or equal to (≥) 50% increase in greatest diameter of any previously noted lesion; 2) a ≥ 50% increase in previously noted HM/SM, or new appearance of HM/SM; 3) a ≥ 50% increase in blood lymphocyte count with at least 5000 B lymphocytes/µL; 4) transformation to a more aggressive histology, e.g., Richter's syndrome; or 5) occurrence of cytopenia attributable to CLL. SD was defined by the absence of necessary criteria to achieve CR or PR, but no advancement to PD. Relapse was defined by a previously noted CR or PR with advancement to PD after a period of ≥ 6 months. Nodular PR was defined by the presence of residual lymphoid nodules.
Time Frame	Month 10
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: Induction Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8.

Measured Values

	CLB + R: Induction Treatment
Number of Participants Analyzed	85
Percentage of Participants With CR, CRi, PR, Stable Disease (SD), Progressive Disease (PD), Relapse, or Nodular PR at the End of Induction Treatment [units: percentage of participants]	
CR	16.5
CRi	2.4
PR	60.0
SD	4.7
PD	3.5
Relapse	0.0
Nodular PR	3.5
Unknown	9.4

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With CR, PR, SD, PD, Relapse, or Nodular PR at the End of Study
Measure Description	CR, and PR as previously defined. PD was defined by 1 of the following: 1) lymphadenopathy: any new lesion, HM/SM, or other organ infiltrates, or a ≥ 50% increase in greatest diameter of any previously noted lesion; 2) a ≥50% increase in previously noted HM/SM, or new appearance of HM/SM; 3) a ≥50% increase in blood lymphocyte count with at least 5000 B lymphocytes/µL; 4) transformation to a more aggressive histology, e.g., Richter's syndrome; or 5) occurrence of cytopenia attributable to CLL. SD was defined by the absence of necessary criteria to achieve CR or PR, but no advancement to PD. Relapse was defined by a previously noted CR or PR with advancement to PD after a period of ≥6 months. Nodular PR was defined by the presence of residual lymphoid nodules.
Time Frame	Month 35
Safety Issue?	No

Analysis Population Description

All randomized participants who were assessed at Month 35 were included in the analysis.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	31	28
Percentage of Participants With CR, PR, SD, PD, Relapse, or Nodular PR at the End of Study [units: percentage of participants]		

	CLB + R: Maintenance Treatment	CLB + R: Observation
CR	32.3	21.4
PR	29.0	14.3
SD	3.2	7.1
PD	29.0	39.3
Relapse	6.5	14.3
Nodular PR	0.0	3.6

5. Secondary Outcome Measure:

Measure Title	Number of Participants With Immunophenotypic CR - BM, Immunophenotypic CR - Peripheral Blood (PB), Molecular CR - BM, or Molecular CR - PB at the End of Induction Treatment
Measure Description	Immunophenotypic CR was defined as the absence of minimal residual disease (MRD) evaluated in participants with CR by 4-color flow cytometry of PB and BM B cells to confirm that tissue was comprised of non-CLL cells. Molecular CR was defined as the absence of MRD evaluated in participants with CR by quantitative polymerase chain reaction (PCR) in PB and BM B cells to confirm that tissue was comprised of non-CLL cells.
Time Frame	Month 10
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
CLB + R: Induction Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8.

Measured Values

	CLB + R: Induction Treatment
Number of Participants Analyzed	85

	CLB + R: Induction Treatment
Number of Participants With Immunophenotypic CR - BM, Immunophenotypic CR - Peripheral Blood (PB), Molecular CR - BM, or Molecular CR - PB at the End of Induction Treatment [units: participants]	
Immunophenotypic CR - BM	2
Immunophenotypic CR - PB	3
Molecular CR - BM	0
Molecular CR - PB	0

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With CR, CRi, PR, SD, PD, or Relapse at the End of Study
Measure Description	CR, CRi, PR, SD, PD, relapse, and nodular PR as previously defined.
Time Frame	Month 35
Safety Issue?	No

Analysis Population Description

All randomized participants.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	34	32
Percentage of Participants With CR, CRi, PR, SD, PD, or Relapse at the End of Study [units: percentage of participants]		
CR	29.4	18.7
CRi	0.0	0.0
PR	26.4	12.5

7. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Immunophenotypic CR - BM or Immunophenotypic CR - PB at the End of Study
Measure Description	Immunophenotypic CR was defined as the absence of MRD evaluated in participants who achieved CR by 4-color flow cytometry of PB and BM B cells to confirm that tissue was comprised of non-CLL cells.
Time Frame	Month 35
Safety Issue?	No

Analysis Population Description

All randomized participants, only participants with a confirmed CR were included in the analysis.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.

Measured Values

	CLB + R: Maintenance Treatment
Number of Participants Analyzed	10

	CLB + R: Maintenance Treatment
Percentage of Participants With Immunophenotypic CR - BM or Immunophenotypic CR - PB at the End of Study [units: percentage of participants]	
Immunophenotypic CR - BM	10.0
Immunophenotypic CR - PB	30.0

8. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Molecular CR - BM or Molecular CR - PB at the End of Study
Measure Description	Molecular CR was defined as the absence of MRD evaluated in participants who achieved CR by quantitative PCR in PB and BM B cells to confirm that tissue was comprised of non-CLL cells.
Time Frame	Month 35
Safety Issue?	No

Analysis Population Description

All randomized participants analyzed for the given parameter at the specified timepoint.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.

Measured Values

	CLB + R: Maintenance Treatment
Number of Participants Analyzed	3
Percentage of Participants With Molecular CR - BM or Molecular CR - PB at the End of Study [units: percentage of participants]	
Molecular CR - BM	100.0

	CLB + R: Maintenance Treatment
Molecular CR - PB	33.3

9. Secondary Outcome Measure:

Measure Title	Number of Participants With Disease Progression, Relapse, Death, Withdrawal Because of an Adverse Event (AE), or New CLL Treatment
Measure Description	Event-free Survival (EFS) was defined as the time from the first dose of study treatment to the date of first documentation of disease progression, relapse for participants with previous CR, death due to any cause, withdrawal due to AE, or beginning new CLL treatment. CR and PD as previously defined. Participants were censored at the time of data cut-off to the most recent date of disease assessment. Participants without a post-BL disease assessment were censored at the time of first dose of study treatment.
Time Frame	Screening, Days 1 and 15 of Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Number of Participants With Disease Progression, Relapse, Death, Withdrawal Because of an Adverse Event (AE), or New CLL Treatment [units: participants]	43

10. Secondary Outcome Measure:

Measure Title	EFS
Measure Description	The median time, in days, from the the date of first dose of study treatment to the date of first documentation of disease progression, relapse for participants with CR, death due to any cause, withdrawal due to AE, or new CLL treatment. CR and PD as previously defined. Participants were censored at the time of data cut-off to the most recent date of disease assessment. Participants without a post-BL disease assessment were censored at the time of first dose if study treatment. The 95% CI was determined using Kaplan-Meier methodology.
Time Frame	Screening, Days 1 and 15 of Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
EFS [units: days] Median (95% Confidence Interval)	1051 (768 to 1164)

11. Secondary Outcome Measure:

Measure Title	Number of Participants With Disease Progression or Death

Measure Description	Progression-free survival (PFS) was defined as the time from the first dose of study treatment to the first documentation of disease progression or death. PD as previously defined. Participants who were withdrawn from the study without documented disease progression were censored at the date of the last tumor assessment when the participant was known to be progression-free. Participants without a post-BL tumor assessment, but known to be alive, were censored at the time of the first dose of study treatment.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Number of Participants With Disease Progression or Death [units: participants]	35

12. Secondary Outcome Measure:

Measure Title	PFS
Measure Description	The median time, in days, from the date of the first dose of study treatment to the date of first documentation of disease progression or death. CR and PD as previously defined. Participants who were withdrawn from the study without documented disease progression were censored at the date of the last tumor assessment when the participant was known to be progression-free. Participants without a post-BL tumor assessment, but known to be alive, were censored at the time of the first dose of study treatment. The 95% CI was determined using Kaplan-Meier methodology.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
PFS [units: days] Median (95% Confidence Interval)	1059 (1010 to 1205)

13. Secondary Outcome Measure:

Measure Title	Number of Participants With New CLL Treatment or Death
Measure Description	Time to new CLL treatment (TTNT) was defined as the time from the first dose of study treatment to the date of new CLL treatment received or the date of death from any cause. Participants who did not receive new CLL treatment and were alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description
ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Number of Participants With New CLL Treatment or Death [units: participants]	22

14. Secondary Outcome Measure:

Measure Title	Time to Next Treatment (TTNT)
Measure Description	The mean time, in days, from the date of the first dose of study treatment to the date of new CLL treatment or the date of death from any cause. Participants who did not receive new CLL treatment and were alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment. Mean survival time and it's standard error (SE) were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Time to Next Treatment (TTNT) [units: days] Mean (Standard Error)	1048.19 (31.86)

15. Secondary Outcome Measure:

Measure Title	Number of Participants Who Died
Measure Description	Overall Survival (OS) was defined as the time from the date of the first dose of study treatment to the date of death due to any cause. Participants were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
Number of Participants Who Died [units: participants]	8

16. Secondary Outcome Measure:

Measure Title	OS
Measure Description	The mean time, in days, from the date of the first dose of study treatment to the date of death due to any cause. Participants were censored at the date of the last follow-up assessment. Participants without a follow-up assessment were censored at the day of last dose of study treatment. The mean survival time and it's SE were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

ITT population

Reporting Groups

	Description
CLB + R: All Participants	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.

Measured Values

	CLB + R: All Participants
Number of Participants Analyzed	85
OS [units: days] Mean (Standard Error)	1135.04 (24.25)

17. Secondary Outcome Measure:

Measure Title	Number of Participants With PD or Death After a Confirmed CR, CRi, or PR
Measure Description	Duration of response was defined as the time from the date of the first documented CR, CRi, or PR to the date of disease progression or death. CR, CRi, PR, and PD as previously defined. Participants with no documented PD after CR, CRi, or PR were censored at the last date at which they were known to have had CR, CRi, or PR, respectively.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description
All randomized participants.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	34	32
Number of Participants With PD or Death After a Confirmed CR, CRi, or PR [units: participants]	11	15

18. Secondary Outcome Measure:

Measure Title	Duration of Response

Measure Description	The mean time, in days, from the date of first documented CR, CRi or PR to the date disease progression or death. CR, CRi, PR, and PD as previously defined. Participants with no documented PD after CR, CRi, or PR were censored at the last date at which they were known to have had CR, CRi, or PR, respectively.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

All randomized participants.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	34	32
Duration of Response [units: days] Mean (Standard Error)	840.87 (29.71)	747.82 (55.77)

Statistical Analysis 1 for Duration of Response

Statistical Analysis Overview	Comparison Groups	CLB + R: Maintenance Treatment, CLB + R: Observation
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2712
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

19. Secondary Outcome Measure:

Measure Title	Number of Participants With PD or Death After a Confirmed CR/CRi
Measure Description	Disease-free survival was defined at the time from the date of first documented CR or CRi to the date of disease progression or death. CR, CRi, and PD as previously defined. Participants with no documented PD after CR or CRi were censored on the last date at which they were known to have had CR or CRi.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

All randomized participants with a confirmed CR or CRi were included in the analysis.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	16	15

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants With PD or Death After a Confirmed CR/CRi [units: participants]	2	8

20. Secondary Outcome Measure:

Measure Title	Disease-Free Survival
Measure Description	The mean time, in days, from the date of first documented CR or CRi to the date of disease progression or death. CR, CRi, and PD as previously defined. Participants with no documented PD after CR or CRi were censored on the last date at which they were known to have had CR or CRi. In both groups, the mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.
Time Frame	Screening, Day 1 Courses 1-8 (4-week courses) and Day 1 of Courses 10-35 (4-week courses) for up to 35 months.
Safety Issue?	No

Analysis Population Description

All randomized participants.

Reporting Groups

	Description
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Measured Values

	CLB + R: Maintenance Treatment	CLB + R: Observation
Number of Participants Analyzed	34	32

	CLB + R: Maintenance Treatment	CLB + R: Observation
Disease-Free Survival [units: days] Mean (Standard Error)	699.91 (68.89)	732.28 (63.37)

Reported Adverse Events

Time Frame	Adverse events (AEs) were recorded from Screening through the Final Visit or withdrawal from study, approximately 35 months.
Additional Description	All participants who received at least 1 dose of chlorambucil or rituximab were included in the analysis.

Reporting Groups

	Description
CLB + R: Induction Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive either rituximab, 375 mg/m^2, IV, once every 8 weeks for up to 24 months (up to 12 infusions), or to be observed for up to 24 months with no further treatment.
CLB + R: Maintenance Treatment	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to receive rituximab, 375 mg/m^2, IV, once every 8 weeks for a total of 12 infusions for up to 24 months.
CLB + R: Observation	Participants completed an 8-month induction treatment phase where they received 8 (4-week) courses of treatment consisting of: CLB, 8 mg/m^2, PO as film-coated tablets, daily (dose could be divided in halves or thirds to prevent nausea), on Days 1-7 of Courses 1 and 2, Days 2-8 of Course 3, and Days 1-7 of Courses 4-8; and rituximab, 375 mg/m^2, IV, on Day 1 of Course 3, and 500 mg/m^2, IV, on Day 1 of Courses 4-8. Participants with CR, CRi, or PR were randomized to be observed for up to 24 months and received no further treatment.

Serious Adverse Events

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	17/97 (17.53%)	4/34 (11.76%)	4/32 (12.5%)
Blood and lymphatic system disorders			
Anaemia [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Haemolytic anaemia [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Haemorrhagic anaemia [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Neutropenia [A] *	1/97 (1.03%)	1/34 (2.94%)	0/32 (0%)
Cardiac disorders			
Atrial fibrillation [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Cardiac failure [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Gastrointestinal disorders			
Diarrhoea [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
General disorders			
Death [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Pyrexia [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Infections and infestations			
Herpes zoster oticus [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Pneumonia [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Injury, poisoning and procedural complications			
Femur fracture [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Hand fracture [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Upper limb fracture [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Musculoskeletal and connective tissue disorders			
Back pain [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma [A] *	0/97 (0%)	1/34 (2.94%)	1/32 (3.12%)
Endometrial cancer [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Mixed oligo-astrocytoma [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Porocarcinoma [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Squamous cell carcinoma of skin [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Nervous system disorders			
Epilepsy [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Transient ischaemic attack [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Respiratory, thoracic and mediastinal disorders			
Pleural effusion [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Skin and subcutaneous tissue disorders			
Rash erythematous [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Toxic skin eruption [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (12.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	73/97 (75.26%)	25/34 (73.53%)	17/32 (53.12%)
Blood and lymphatic system disorders			
Anaemia [A] *	14/97 (14.43%)	0/34 (0%)	1/32 (3.12%)
Haemolytic anaemia [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Leukopenia [A] *	5/97 (5.15%)	1/34 (2.94%)	0/32 (0%)
Lymphadenopathy [A] *	2/97 (2.06%)	2/34 (5.88%)	4/32 (12.5%)
Lymphocytosis [A] *	0/97 (0%)	0/34 (0%)	2/32 (6.25%)
Lymphopenia [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Neutropenia [A] *	31/97 (31.96%)	5/34 (14.71%)	1/32 (3.12%)
Splenomegaly [A] *	1/97 (1.03%)	0/34 (0%)	2/32 (6.25%)
Thrombocytopenia [A] *	16/97 (16.49%)	1/34 (2.94%)	1/32 (3.12%)
Cardiac disorders			
Angina pectoris [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Atrial fibrillation [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Hypertensive cardiomyopathy [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Sinus tachycardia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Tachycardia [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Ear and labyrinth disorders			
Hypoacusis [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Vertigo [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Endocrine disorders			
Thyroid disorder [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Thyroiditis [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Gastrointestinal disorders			
Abdominal distension [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Abdominal pain [A] *	3/97 (3.09%)	0/34 (0%)	0/32 (0%)
Abdominal pain upper [A] *	1/97 (1.03%)	1/34 (2.94%)	0/32 (0%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Colitis [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Constipation [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Diarrhoea [A] *	4/97 (4.12%)	0/34 (0%)	0/32 (0%)
Dyskinesia oesophageal [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Dyspepsia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Flatulence [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Gastritis [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Hiatus hernia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Intestinal obstruction [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Nausea [A] *	7/97 (7.22%)	0/34 (0%)	1/32 (3.12%)
Reflux oesophagitis [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Tongue dry [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Vomiting [A] *	4/97 (4.12%)	0/34 (0%)	0/32 (0%)
General disorders			
Asthenia [A] *	4/97 (4.12%)	1/34 (2.94%)	0/32 (0%)
Chest pain [A] *	3/97 (3.09%)	0/34 (0%)	0/32 (0%)
Chills [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Cyst [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Face oedema [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Fatigue [A] *	5/97 (5.15%)	0/34 (0%)	3/32 (9.38%)
Hyperpyrexia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Influenza like illness [A] *	3/97 (3.09%)	0/34 (0%)	1/32 (3.12%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Infusion related reaction [A] *	6/97 (6.19%)	0/34 (0%)	0/32 (0%)
Mucosal inflammation [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Oedema peripheral [A] *	2/97 (2.06%)	2/34 (5.88%)	0/32 (0%)
Pain [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Pyrexia [A] *	11/97 (11.34%)	0/34 (0%)	2/32 (6.25%)
Hepatobiliary disorders			
Hepatomegaly [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Immune system disorders			
Hypersensitivity [A] *	1/97 (1.03%)	1/34 (2.94%)	0/32 (0%)
Multiple allergies [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Infections and infestations			
Bronchitis [A] *	0/97 (0%)	4/34 (11.76%)	1/32 (3.12%)
Cellulitis [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Conjunctivitis bacterial [A] *	1/97 (1.03%)	2/34 (5.88%)	0/32 (0%)
Cystitis [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Fungal infection [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Gastroenteritis [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Hepatitis B [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Herpes simplex [A] *	3/97 (3.09%)	0/34 (0%)	1/32 (3.12%)
Herpes zoster [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Herpes zoster oticus [A] *	1/97 (1.03%)	1/34 (2.94%)	2/32 (6.25%)
Nasopharyngitis [A] *	2/97 (2.06%)	1/34 (2.94%)	1/32 (3.12%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pharyngitis [A] *	2/97 (2.06%)	0/34 (0%)	1/32 (3.12%)
Pilonidal cyst [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Productive cough [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Pyrexia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Tooth abscess [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Injury, poisoning and procedural complications			
Arthropod bite [A] *	1/97 (1.03%)	1/34 (2.94%)	0/32 (0%)
Humerus fracture [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Spinal compression fracture [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Investigations			
Blood creatine increased [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Blood lactate dehydrogenase increased [A] *	0/97 (0%)	2/34 (5.88%)	0/32 (0%)
Breath sounds abnormal [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Platelet count decreased [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Transaminases increased [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Weight decreased [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Metabolism and nutrition disorders			
Anorexia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Decreased appetite [A] *	0/97 (0%)	0/34 (0%)	2/32 (6.25%)
Diabetes mellitus [A] *	2/97 (2.06%)	0/34 (0%)	1/32 (3.12%)
Dyslipidaemia [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Hyperuricaemia [A] *	1/97 (1.03%)	1/34 (2.94%)	2/32 (6.25%)
Musculoskeletal and connective tissue disorders			

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Arthralgia [A] *	2/97 (2.06%)	1/34 (2.94%)	0/32 (0%)
Back pain [A] *	4/97 (4.12%)	2/34 (5.88%)	0/32 (0%)
Bone pain [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Musculoskeletal pain [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Pain in extremity [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Pain in jaw [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Nervous system disorders			
Dizziness [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Headache [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Memory impairment [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Neuropathy peripheral [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Paraesthesia [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Syncope [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Renal and urinary disorders			
Bladder disorder [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Dysuria [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Micturition urgency [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Reproductive system and breast disorders			
Benign prostatic hyperplasia [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Gynaecomastia [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Peyronie's disease [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] *	5/97 (5.15%)	3/34 (8.82%)	1/32 (3.12%)

	CLB + R: Induction Treatment	CLB + R: Maintenance Treatment	CLB + R: Observation
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A] *	3/97 (3.09%)	0/34 (0%)	0/32 (0%)
Nasal septum perforation [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Oropharyngeal discomfort [A] *	2/97 (2.06%)	0/34 (0%)	1/32 (3.12%)
Tonsillar hypertrophy [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Skin and subcutaneous tissue disorders			
Erythema [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Hyperhidrosis [A] *	1/97 (1.03%)	0/34 (0%)	1/32 (3.12%)
Night sweats [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Pemphigoid [A] *	0/97 (0%)	1/34 (2.94%)	0/32 (0%)
Pruritus [A] *	5/97 (5.15%)	0/34 (0%)	0/32 (0%)
Rash [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Rash erythematous [A] *	2/97 (2.06%)	0/34 (0%)	0/32 (0%)
Skin lesion [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Surgical and medical procedures			
Haemorrhoid operation [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Knee operation [A] *	0/97 (0%)	0/34 (0%)	1/32 (3.12%)
Vascular disorders			
Carotid artery stenosis [A] *	0/97 (0%)	1/34 (2.94%)	1/32 (3.12%)
Deep vein thrombosis [A] *	1/97 (1.03%)	0/34 (0%)	0/32 (0%)
Hypertension [A] *	2/97 (2.06%)	2/34 (5.88%)	1/32 (3.12%)
Hypotension [A] *	3/97 (3.09%)	0/34 (0%)	0/32 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA (12.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

Results Point of Contact:

Name/Official Title: Medical Communications
Organization: Hoffman-LaRoche
Phone: 800-821-8590
Email: genentech@druginfo.com