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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

LFA102

Trial Indications

Adult patients with castration-resistant prostate cancer (CRPC) or metastatic breast cancer (MBC) or uterine leiomyoma (UL).

Protocol Number

CLFA102X2102

Protocol Title

A Phase I, multicenter, open-label study of LFA102 administered intravenously in patients with prolactin receptor-positive castration-resistant prostate cancer or prolactin receptor-positive metastatic breast cancer.

Clinical Trial Study Phase

Phase I

Study Start/End Dates

First patient first visit: 27-Sep-2011

Last patient last visit: 06-Mar-2014 (Terminated Study)

Reason for Termination

The lack of anti-tumor efficacy of LFA102 (no Prostate specific antigen (PSA) response for CRPC patients group and no response (partial response or better) for MBC patients group), resulted in the decision of termination of this study.

Additionally, due to difficult enrollment, no UL patients were enrolled in the study.

Study Design/Methodology

This was a Phase I open-label, multi-center study consisting of a dose escalation phase and an expansion phase in adult patients with CRPC or MBC. LFA102 was administered intravenously once every 4 weeks during the treatment period (28-days treatment cycle). All patients were treated until they met the criteria for study discontinuation (e.g. disease progression, adverse event (AE), unacceptable toxicity, patient withdrawal) or study closure.

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Centers

Nine sites in 4 countries: USA (5), Belgium (2), Italy (1) and Spain (1).

Publication

None

Objectives:

Primary objective:

Dose escalation: To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of LFA102 as a single agent when administered as intravenous (iv) to adult patients with CRPC or MBC.

Dose expansion: To characterize the safety and tolerability of LFA102 in CRPC, MBC, or UL patients.

Secondary objective:

Dose escalation and dose expansion:

1. To characterize pharmacokinetics (PK) of LFA102.
2. Disease response for:
    - **Prostate cancer**: To assess preliminary anti-tumor activity of LFA102 as a single agent when administered as iv to adult patients with CRPC.
    - **Breast cancer**: To assess preliminary anti-tumor activity of LFA102 as a single agent when administered as iv to adult patients with MBC.
    - **Uterine leiomyoma**: To assess preliminary anti-tumor activity of LFA102 as a single agent when administered as iv to adult patients with UL.
3. To assess any emergence of anti-LFA102 antibodies.

Due to difficult enrollment, no UL patients were enrolled in the study.

Test Product, Doses, and Mode of Administration

LFA102 was administred intravenously at doses of 3 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg and 60 mg/kg.

Statistical Methods

Due to lack of efficacy of LFA102 in MBC and CRPC patients, only study results needed for abbreviated Clinical study report were summarized and all other data were just listed.

The number of patients who were enrolled and treated as well as those who discontinued the study (along with their reasons for premature discontinuation) were summarized by treatment and overall. All protocol deviations were listed. Demographic and other baseline data (e.g., age, gender, height, weight, medical conditions, medical history, Eastern Cooperative Oncology Group (ECOG) performance status) were summarized descriptively by treatment

group and overall using the Full Analysis Set (FAS). Past and current medical history, prior anti-neoplastic therapy, diagnosis and extent of cancer were listed by treatment.

Exposure to LFA102 was to be listed by patient and summarized by treatment group and by disease type. Concomitant therapy and significant non-drug therapies prior to the start of LFA102, after the start of LFA102 and antineoplastic therapies since discontinuation of LFA102 were listed by patient and summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and treatment group by means of contingency tables.

MTD determination: Estimation of the MTD during the dose escalation phase of the study was based upon the estimation of the probability distribution of the incidence of dose limiting toxicities (DLT) in Cycle 1 in patients in the dose determining set (DDS). The primary endpoint in the dose escalation phase was the occurrence of DLT in Cycle 1 (i.e. absence or presence of DLT). During dose escalation phase, MTD were not reached and no DLTs occurred during the study.

Pharmacokinetics: The pharmacokinetic analysis set was used for LFA102 serum concentration and PK parameters analyses. Cmax (maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after dose administration) and AUClast (area under the curve (AUC) from time zero to the last quantifiable concentration point) were used for an informal dose proportionality analysis using the power model (Gough et al 1995). Both PK parameters and dose levels were analyzed on the log scale.

Efficacy and biomarker: Due to lack of efficacy effect, the exploratory biomarker analysis (except serum prolactin) correlated with efficacy mentioned in the protocol was not performed and all the efficacy, immunogenicity and biomarker data were listed.

Safety: Data from patients of the expansion phase was pooled with the patients of the escalation phase receiving the same dose; there was no separate analysis conducted.

All safety data were reviewed including all observed AEs, in particular serious/clinically significant events, deaths, abnormal laboratory values, vital signs, physical examination and other safety assessments (e.g. electrocardiogram (ECG), etc.).

Study Population: Key Inclusion/Exclusion Criteria

For all indications

- Age ≥ 18 years
- ECOG performance status grade ≤ 2
- Life expectancy ≥ 12 weeks
- Suitable venous access for blood sampling
- Anticoagulation was allowed if patients were already on a stable dose of warfarin or on a stable dose of low molecular weight heparin for >2 weeks at time of dose initiation.
- Concomitant use of bisphosphonates and other bone supportive agents was allowed if the dose and renal function have been stable for at least 12 weeks before the enrollment and no related side–effects ≥ grade 2 were present for at least 4 weeks prior to study drug treatment.

- Must weigh 480 kg or less if treated with LFA102 at 20 mg/kg, 240 kg or less for patients dosed at 40 mg/kg, 160 kg or less for patients dosed at 60 mg/kg.

Prostate cancer

- Histologically confirmed diagnosis of prostate adenocarcinoma.
- Detectable metastases by bone scan, Computed Tomography-scan, or magnetic resonate imaging (MRI).
- Available tumor specimen (primary or metastatic, archival or fresh) is mandatory at Screening/Baseline visit for analysis.
- Documented castration condition defined by a serum testosterone levels of <50 ng/dl (1.7 nmol/L). The castration condition can be obtained by orchiectomy or use of luteinizing hormone-releasing hormone (LHRH) agonists or antagonists; patients who had not undergone surgical orchiectomy were willing to continue LHRH agonists and antagonist during the course of the study.
- Documented progressive disease following the previous line of therapy for which Prostate Cancer Clinical Trials Working Group (PCWG2) criteria were used to define progression:
    - For patients who manifest disease progression solely as a rising prostate specific antigen (PSA) level, PCWG2 requires a sequence of rising PSA values on 2 consecutive occasions at least 1 week apart (but not limited to the 30 day screening period) and a minimum value of 2.0 ng/mL. Most recent PSA level was to be obtained within 21 days prior to first study drug treatment.
    - Note: for patients receiving flutamide, at least one of the PSA values was to be obtained 4 weeks or more after flutamide discontinuation. For patients receiving bicalutamide or nilutamide, at least one of the PSA values was to be obtained 6 weeks or more after anti-androgen discontinuation.
    - In the presence of measurable nodal or visceral lesions documented progression of one of these lesions was sufficient for eligibility independent of PSA. In case of lymph node ≥ 15 mm in diameter, it was considered measurable and used to evaluate change of size.
    - As for bone metastases, progression was defined by the appearance of 2 or more new lesions by bone scan or other scan (e.g. MRI).
- Anti-androgen withdrawal followed by progression took place at least ≥ 4 weeks (≥ 6 weeks for bicalutamide or nilutamide) before enrollment.
- Minimum washout period of 4 weeks after the use of prostate cancer therapy (cytotoxic, biologic, other therapies) and 6 weeks after stopping the antiandrogens bicalutamide or nilutamide. LHRH agonists or antagonists were to be continued.

For breast cancer

- Histologically or cytologically confirmed locally advanced or metastatic breast cancer with documentation of estrogen and progesterone receptors (ER/PR) and Human epidermal growth factor receptor 2 (HER-2) /neu status as defined by American Society of Clinical Oncology- College of American Pathologists (ASCO-CAP) guidelines.

- Available tumor specimen (primary or metastatic, archival or fresh) was mandatory at Screening/Baseline visit for analysis.
- Progressed following last line of treatment in the locally advanced or metastatic setting.
- For Dose Escalation: Presence of at least one measurable or non-measurable lesion as defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
- For Dose Expansion: Presence of at least one measurable lesion as defined by RECIST (v1.5).
- Note: In case of a single lesion, confirmation of breast cancer was needed.
- Discontinued chemotherapy, hormone therapy, or targeted anticancer therapy ≥ 4 weeks (≥ 6 weeks for nitrosourea, antibodies, or mitomycin-C) prior to starting study drug and who had recovered from side effects to grade 1 or baseline values.

Organ function and laboratory results

- Laboratory values:
  - Absolute neutrophil count (ANC) ≥ 1.5×10^{9}/L
  - Hemoglobin (Hgb) ≥ 9 g/dL (may have been transfused)
  - Platelets ≥ 90×10^{9}/L
  - Total serum bilirubin ≤ 1.5×ULN (upper limit of normal) (In patients with known Gilbert syndrome, total bilirubin ≤ 3×ULN, with direct bilirubin ≤ 1.5×ULN)
  - AST (SGOT) and ALT (SGPT) ≤ 2.5×ULN, except for patients with tumor involvement of the liver who must have AST and ALT ≤ 5×ULN
  - Serum creatinine ≤ 1.5×ULN or creatinine clearance (CrCL) ≥ 50 mL/min (from calculated via Cockcroft-Gault formula or 24 hr urine collection)

Informed consent

- Patient was capable of understanding and complying with the protocol and has signed the informed consent document.

For prostate and breast cancer indications:

- Prolactin receptor (PRLR)-positive primary or metastatic tumor as determined by Immunohistochemistry (IHC) in archival or fresh biopsy tissue sample (Dose Escalation only).

Participant Flow Table

Patient disposition by treatment dose group (FAS)

	LFA102 3 mg/kg N=3 n (%)	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
Patients treated	3 (100)	3 (100)	7 (100)	8 (100)	52 (100)	73 (100)
Treatment discontinued						
Primary reason for end of treatment						
Adverse Events	0	0	1 (14.3)	1 (12.5)	3 (5.8)	5 (6.8)

	LFA102 3 mg/kg N=3 n (%)	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
Disease progression	3 (100)	3 (100)	6 (85.7)	7 (87.5)	48 (92.3)	67 (91.8)
Patient withdrew consent	0	0	0	0	1 (1.9)	1 (1.4)
Primary reason for study evaluation completion						
Death	0	0	2 (28.6)	0	2 (3.8)	4 (5.5)
Follow-up phase completed as per protocol	3 (100)	3 (100)	5 (71.4)	8 (100)	47 (90.4)	66 (90.4)
Lost to follow-up	0	0	0	0	2 (3.8)	2 (2.7)
Patient withdrew consent	0	0	0	0	1 (1.9)	1 (1.4)

Study evaluation completion corresponds to the evaluation performed on 30-day following treatment discontinuation.

Baseline Characteristics

Demographic summary by treatment dose group (FAS)

	LFA102 3 mg/kg N=3	LFA102 10 mg/kg N=3	LFA102 20 mg/kg N=7	LFA102 40 mg/kg N=8	LFA102 60 mg/kg N=52	All Patients N=73
Age (Years)						
n	3	3	7	8	52	73
Mean	76.7	70.3	57.3	68.6	64.5	65.0
SD	4.93	12.42	9.66	9.61	10.92	10.98
Median	79.0	77.0	55.0	69.0	65.5	66.0
Minimum	71.0	56.0	45.0	52.0	41.0	41.0
Maximum	80.0	78.0	76.0	85.0	89.0	89.0
Age category (Years) – n (%)						
<65	0	1 (33.3)	6 (85.7)	3 (37.5)	25 (48.1)	35 (47.9)
≥ 65	3 (100)	2 (66.7)	1 (14.3)	5 (62.5)	27 (51.9)	38 (52.1)
Sex- n (%)						
Female	0	2 (66.7)	4 (57.1)	2 (25.0)	26 (50.0)	34 (46.6)
Male	3 (100)	1 (33.3)	3 (42.9)	6 (75.0)	26 (50.0)	39 (53.4)
Predominant Race-n (%)						
Caucasian	3 (100)	3 (100)	7 (100)	7 (87.5)	48 (92.3)	68 (93.2)
Black	0	0	0	0	4 (7.7)	4 (5.5)
Other	0	0	0	1 (12.5)	0	1 (1.4)
Ethnicity- n (%)						
Hispanic/Latino	0	0	1 (14.3)	1 (12.5)	8 (15.4)	10 (13.7)
Other	3 (100)	3 (100)	6 (85.7)	7 (87.5)	44 (84.6)	63 (86.3)
Weight (kg)						
n	3	3	7	8	52	73
Mean	99.3	88.7	70.7	84.3	80.1	80.8
SD	18.21	30.66	11.87	16.72	19.31	19.16
Median	94.4	73.0	66.7	81.1	78.0	77.5

	LFA102 3 mg/kg	LFA102 10 mg/kg	LFA102 20 mg/kg	LFA102 40 mg/kg	LFA102 60 mg/kg	All Patients
	N=3	N=3	N=7	N=8	N=52	N=73
Minimum	84.1	69.0	60.0	69.0	45.0	45.0
Maximum	119.5	124.0	91.6	119.5	140.0	140.0
Height (cm)						
n	3	3	7	8	51	72
Mean	174.2	166.6	167.0	170.9	168.6	168.9
SD	5.20	4.86	10.13	6.82	10.98	10.09
Median	172.5	168.7	171.0	172.1	169.0	170.0
Minimum	170.0	161.0	153.0	160.0	146.0	146.0
Maximum	180.0	170.0	180.0	179.3	194.0	194.0
Baseline ECOG performance status[a]-n (%)						
0	1 (33.3)	1 (33.3)	3 (42.9)	4 (50.0)	21 (40.4)	30 (41.1)
1	1 (33.3)	2 (66.7)	2 (28.6)	4 (50.0)	29 (55.8)	38 (52.1)
2	1 (33.3)	0	2 (28.6)	0	2 (3.8)	5 (6.8)

[a] 0 - Fully active, able to carry on all pre-disease performance without restriction;
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;
2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours;
3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours;
4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair;
5 – Dead.

Summary of Efficacy

There was no efficacy of LFA102 in MBC and CRPC patients.

Summary of Safety

Summary of MTD or RDE determination

During dose escalation phase, MTD were not reached and no DLTs occurred during the study. The RDE was established at 60 mg/kg based on the results: a linear relationship between LFA102 dose and AUC as well as Cmax was observed up to 40 mg/kg. Both AUC and Cmax were relatively proportional at the tested doses (3 mg/kg to 60 mg/kg dose. Similarly, trough concentrations increased dose proportionally up to 40 mg/kg. Only a minor increase in trough concentrations was observed upon dose escalation from 40 to 60 mg/kg. The prolactin (PRL) fold change relative to baseline follows the same trend for the PK profile. PRL fold change increases with LFA102 dose level up to 40 mg/kg. Consistent with PK profile, at 60 mg/kg dose level, PRL fold change reached a plateau which suggested saturation of potentially all available PRLR.

This was also supported by the PK and PRL results, the safety and tolerability profile of LFA102 in all the tested doses. The median DLT at 60 mg/kg was estimated to 12.2% by BLRM and the posterior probability of targeted toxicity is 31.5%, which was the highest among the tested doses.

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Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, and treatment dose group (Safety set)

Primary system organ class	LFA102 3 mg/kg N=3 n (%)	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
-Any primary SOC	3 (100.0)	3 (100.0)	7 (100.0)	8 (100.0)	50 (96.2)	71 (97.3)
Blood and lymphatic system disorders	0	0	1 (14.3)	3 (37.5)	12 (23.1)	16 (21.9)
Cardiac disorders	0	1 (33.3)	1 (14.3)	2 (25.0)	6 (11.5)	10 (13.7)
Ear and labyrinth disorders	0	1 (33.3)	1 (14.3)	1 (12.5)	2 (3.8)	5 (6.8)
Endocrine disorders	0	0	0	0	2 (3.8)	2 (2.7)
Eye disorders	0	1 (33.3)	1 (14.3)	2 (25.0)	4 (7.7)	8 (11.0)
Gastrointestinal disorders	2 (66.7)	2 (66.7)	4 (57.1)	7 (87.5)	29 (55.8)	44 (60.3)
General disorders and administration site conditions	1 (33.3)	1 (33.3)	4 (57.1)	5 (62.5)	34 (65.4)	45 (61.6)
Hepatobiliary disorders	0	0	1 (14.3)	0	0	1 (1.4)
Infections and infestations	0	0	1 (14.3)	2 (25.0)	20 (38.5)	23 (31.5)
Injury, poisoning and procedural complications	1 (33.3)	1 (33.3)	1 (14.3)	0	3 (5.8)	6 (8.2)
Investigations	1 (33.3)	2 (66.7)	2 (28.6)	5 (62.5)	25 (48.1)	35 (47.9)
Metabolism and nutrition disorders	0	3 (100.0)	3 (42.9)	5 (62.5)	21 (40.4)	32 (43.8)
Musculoskeletal and connective tissue disorders	3 (100.0)	1 (33.3)	2 (28.6)	5 (62.5)	31 (59.6)	42 (57.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	4 (7.7)	4 (5.5)
Nervous system disorders	1 (33.3)	1 (33.3)	1 (14.3)	3 (37.5)	20 (38.5)	26 (35.6)
Psychiatric disorders	0	0	2 (28.6)	1 (12.5)	14 (26.9)	17 (23.3)
Renal and urinary disorders	0	0	2 (28.6)	1 (12.5)	9 (17.3)	12 (16.4)
Reproductive system and breast disorders	0	1 (33.3)	1 (14.3)	0	2 (3.8)	4 (5.5)
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	2 (28.6)	1 (12.5)	15 (28.8)	19 (26.0)
Skin and subcutaneous tissue disorders	1 (33.3)	1 (33.3)	0	3 (37.5)	9 (17.3)	14 (19.2)
Vascular disorders	1 (33.3)	1 (33.3)	2 (28.6)	0	6 (11.5)	10 (13.7)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 30(+2) days of the last study medication are reported.

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All and Grade3/4 adverse events, regardless of study drug relationship, by PT and treatment dose group- (more than or equal to 5% for all grades or more than or equal to 2% for grade3/4 events for all patients) (Safety set)

	LFA102 3 mg/kg N=3		LFA102 10 mg/kg N=3		LFA102 20 mg/kg N=7		LFA102 40 mg/kg N=8		LFA102 60 mg/kg N=52		All Patients N=73	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
- Total	3 (100.0)	1 (33.3)	3 (100.0)	2 (66.7)	7 (100.0)	3 (42.9)	8 (100.0)	6 (75.0)	50 (96.2)	25 (48.1)	71 (97.3)	37 (50.7)
Fatigue	1 (33.3)	0	1 (33.3)	0	2 (28.6)	0	4 (50.0)	1 (12.5)	24 (46.2)	5 (9.6)	32 (43.8)	6 (8.2)
Nausea	1 (33.3)	0	2 (66.7)	0	2 (28.6)	1 (14.3)	3 (37.5)	0	16 (30.8)	0	24 (32.9)	1 (1.4)
Constipation	1 (33.3)	0	0	0	1 (14.3)	0	1 (12.5)	0	12 (23.1)	1 (1.9)	15 (20.5)	1 (1.4)
Decreased appetite	0	0	1 (33.3)	0	2 (28.6)	0	2 (25.0)	0	10 (19.2)	3 (5.8)	15 (20.5)	3 (4.1)
Vomiting	0	0	1 (33.3)	0	3 (42.9)	0	0	0	11 (21.2)	0	15 (20.5)	0
Pain in extremity	2 (66.7)	0	1 (33.3)	0	0	0	1 (12.5)	0	9 (17.3)	1 (1.9)	13 (17.8)	1 (1.4)
Anemia	0	0	0	0	1 (14.3)	0	2 (25.0)	0	9 (17.3)	2 (3.8)	12 (16.4)	2 (2.7)
Aspartate aminotransferase increased	0	0	0	0	1 (14.3)	1 (14.3)	2 (25.0)	1 (12.5)	8 (15.4)	2 (3.8)	11 (15.1)	4 (5.5)
Asthenia	0	0	0	0	2 (28.6)	1 (14.3)	1 (12.5)	1 (12.5)	7 (13.5)	3 (5.8)	10 (13.7)	5 (6.8)
Back pain	1 (33.3)	0	0	0	1 (14.3)	0	1 (12.5)	0	7 (13.5)	2 (3.8)	10 (13.7)	2 (2.7)
Weight decreased	0	0	0	0	1 (14.3)	1 (14.3)	2 (25.0)	0	7 (13.5)	0	10 (13.7)	1 (1.4)
Alanine aminotransferase increased	0	0	0	0	0	0	2 (25.0)	0	7 (13.5)	1 (1.9)	9 (12.3)	1 (1.4)
Arthralgia	0	0	0	0	0	0	2 (25.0)	0	7 (13.5)	0	9 (12.3)	0
Blood alkaline phosphatase increased	0	0	0	0	1 (14.3)	1 (14.3)	1 (12.5)	1 (12.5)	7 (13.5)	1 (1.9)	9 (12.3)	3 (4.1)
Diarrhea	1 (33.3)	0	0	0	0	0	4 (50.0)	1 (12.5)	4 (7.7)	0	9 (12.3)	1 (1.4)
Gamma-glutamyltransferase increased	0	0	0	0	0	0	1 (12.5)	1 (12.5)	7 (13.5)	2 (3.8)	8 (11.0)	3 (4.1)
Headache	0	0	1 (33.3)	0	0	0	0	0	7 (13.5)	1 (1.9)	8 (11.0)	1 (1.4)

	LFA102 3 mg/kg N=3		LFA102 10 mg/kg N=3		LFA102 20 mg/kg N=7		LFA102 40 mg/kg N=8		LFA102 60 mg/kg N=52		All Patients N=73	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Insomnia	0	0	0	0	0	0	0	0	8 (15.4)	0	8 (11.0)	0
Muscular weakness	0	0	0	0	0	0	1 (12.5)	0	7 (13.5)	0	8 (11.0)	0
Musculoskeletal pain	0	0	0	0	0	0	1 (12.5)	0	6 (11.5)	1 (1.9)	7 (9.6)	1 (1.4)
Dyspnea	0	0	0	0	1 (14.3)	1 (14.3)	0	0	5 (9.6)	2 (3.8)	6 (8.2)	3 (4.1)
Hypophosphatemia	0	0	1 (33.3)	1 (33.3)	0	0	1 (12.5)	1 (12.5)	4 (7.7)	2 (3.8)	6 (8.2)	4 (5.5)
Pyrexia	0	0	0	0	0	0	1 (12.5)	0	5 (9.6)	0	6 (8.2)	0
Urinary tract infection	0	0	0	0	1 (14.3)	1 (14.3)	0	0	5 (9.6)	0	6 (8.2)	1 (1.4)
Abdominal pain	0	0	0	0	0	0	0	0	5 (9.6)	0	5 (6.8)	0
Anxiety	0	0	0	0	1 (14.3)	0	1 (12.5)	0	3 (5.8)	0	5 (6.8)	0
Hyperglycemia	0	0	0	0	1 (14.3)	0	1 (12.5)	1 (12.5)	3 (5.8)	0	5 (6.8)	1 (1.4)
Oedema peripheral	0	0	0	0	0	0	0	0	5 (9.6)	0	5 (6.8)	0
Amylase increased	0	0	0	0	0	0	0	0	4 (7.7)	0	4 (5.5)	0
Blood prolactin increased	0	0	0	0	0	0	2 (25.0)	0	2 (3.8)	0	4 (5.5)	0
Confusional state	0	0	0	0	0	0	0	0	4 (7.7)	1 (1.9)	4 (5.5)	1 (1.4)
Cough	0	0	1 (33.3)	0	0	0	1 (12.5)	0	2 (3.8)	0	4 (5.5)	0
Dizziness	0	0	0	0	0	0	0	0	4 (7.7)	0	4 (5.5)	0
Hypoalbuminemia	0	0	0	0	1 (14.3)	0	0	0	3 (5.8)	0	4 (5.5)	0
Hypokalemia	0	0	0	0	0	0	0	0	4 (7.7)	1 (1.9)	4 (5.5)	1 (1.4)
Lymphocyte count decreased	0	0	0	0	1 (14.3)	1 (14.3)	0	0	3 (5.8)	1 (1.9)	4 (5.5)	2 (2.7)
Muscle spasms	0	0	0	0	0	0	0	0	4 (7.7)	0	4 (5.5)	0
Musculoskeletal chest pain	0	0	0	0	0	0	1 (12.5)	0	3 (5.8)	0	4 (5.5)	0
Upper respiratory tract infection	0	0	0	0	0	0	2 (25.0)	0	2 (3.8)	0	4 (5.5)	0
Failure to thrive	0	0	0	0	1 (14.3)	1 (14.3)	1 (12.5)	1 (12.5)	1 (1.9)	1 (1.9)	3 (4.1)	3 (4.1)

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Clinical Trial Results Database

	LFA102 3 mg/kg N=3		LFA102 10 mg/kg N=3		LFA102 20 mg/kg N=7		LFA102 40 mg/kg N=8		LFA102 60 mg/kg N=52		All Patients N=73	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Bone pain	0	0	0	0	1 (14.3)	1 (14.3)	1 (12.5)	1 (12.5)	0	0	2 (2.7)	2 (2.7)
Metastases to spine	0	0	0	0	0	0	0	0	2 (3.8)	2 (3.8)	2 (2.7)	2 (2.7)
Myocardial infarction	0	0	1 (33.3)	1 (33.3)	0	0	0	0	1 (1.9)	1 (1.9)	2 (2.7)	2 (2.7)
Performance status decreased	0	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (1.9)	1 (1.9)	2 (2.7)	2 (2.7)

Preferred terms are sorted in descending frequency of All Grades column, as reported in all patients.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
Only AEs occurring during treatment or within 30(+2) days of the last study medication are reported.

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Deaths, by primary system organ class, PT and treatment dose group (Safety set)

Primary system organ class Preferred term	LFA102 20 mg/kg N=7 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
Any primary system organ class-Total	2 (28.6)	2 (3.8)	4 (5.5)
Cardiac disorders	0	1 (1.9)	1 (1.4)
Cardiac arrest	0	1 (1.9)	1 (1.4)
Metabolism and nutrition disorders	1 (14.3)	0	1 (1.4)
Failure to thrive	1 (14.3)	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (14.3)	1 (1.9)	2 (2.7)
Breast cancer	1 (14.3)	1 (1.9)	2 (2.7)

Primary system organ classes are presented alphabetically; PTs are sorted within primary system organ class alphabetically.
Only deaths occurring during treatment or within 30 (+2) days of the last study medication are reported.

Serious Adverse Events regardless of study drug relationship, by primary system organ class, preferred term and treatment dose group (Safety set)

Primary system organ class Preferred term	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
Any primary system organ class - Total	1 (33.3)	3 (42.9)	3 (37.5)	15 (28.8)	22 (30.1)
Cardiac disorders-Total	1 (33.3)	0	0	2 (3.8)	3 (4.1)
Myocardial infarction	1 (33.3)	0	0	1 (1.9)	2 (2.7)
Acute myocardial infarction	0	0	0	1 (1.9)	1 (1.4)
Cardiac arrest	0	0	0	1 (1.9)	1 (1.4)
Gastrointestinal disorders-Total	0	2(28.6)	0	3 (5.8)	5 (6.8)
Nausea	0	1(14.3)	0	1 (1.9)	2 (2.7)
Vomiting	0	1(14.3)	0	1 (1.9)	2 (2.7)
Ascites	0	1(14.3)	0	0	1 (1.4)
Constipation	0	0	0	1 (1.9)	1 (1.4)
Dysphagia	0	0	0	1 (1.9)	1 (1.4)
General disorders and administration site conditions-Total	0	0	1 (12.5)	5 (9.6)	6 (8.2)
Asthenia	0	0	1 (12.5)	1 (1.9)	2 (2.7)
Fatigue	0	0	0	2 (3.8)	2 (2.7)
Pain	0	0	0	2 (3.8)	2 (2.7)
Performance status decreased	0	0	1 (12.5)	1 (1.9)	2 (2.7)
Face edema	0	0	0	1 (1.9)	1 (1.4)
Localized edema	0	0	0	1 (1.9)	1 (1.4)
Pyrexia	0	0	1 (12.5)	0	1 (1.4)
Infections and infestations-Total	0	0	0	5 (9.6)	5 (6.8)
Bronchitis	0	0	0	1 (1.9)	1 (1.4)

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Primary system organ class Preferred term	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)
Clostridium difficile infection	0	0	0	1 (1.9)	1 (1.4)
Pneumonia	0	0	0	1(1.9)	1 (1.4)
Sepsis	0	0	0	1(1.9)	1 (1.4)
Skin infection	0	0	0	1(1.9)	1 (1.4)
Injury, poisoning and procedural complications-Total	0	1 (14.3)	0	0	1 (1.4)
Subdural hematoma	0	1 (14.3)	0	0	1 (1.4)
Investigations-Total	0	0	0	2(3.8)	2 (2.7)
Alanine aminotransferase increased	0	0	0	1(1.9)	1 (1.4)
Aspartate aminotransferase increased	0	0	0	1(1.9)	1 (1.4)
Troponin increased	0	0	0	1 (1.9)	1 (1.4)
Metabolism and nutrition disorders-Total	0	1 (14.3)	1 (12.5)	3 (5.8)	5 (6.8)
Failure to thrive	0	1 (14.3)	1 (12.5)	1 (1.9)	3 (4.1)
Decreased appetite	0	0	0	2 (3.8)	2 (2.7)
Musculoskeletal and connective tissue disorders-Total	0	1 (14.3)	0	1 (1.9)	2 (2.7)
Bone pain	0	1 (14.3)	0	0	1 (1.4)
Musculoskeletal pain	0	0	0	1 (1.9)	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)-Total	0	0	0	3 (5.8)	3 (4.1)
Metastases to spine	0	0	0	2 (3.8)	2 (2.7)
Hemangioma	0	0	0	1 (1.9)	1 (1.4)
Paraneoplastic syndrome	0	0	0	1 (1.9)	1 (1.4)
Nervous system disorders-Total	0	0	2 (25.0)	6 (11.5)	8 (11.0)
Cerebrovascular accident	0	0	1 (12.5)	1 (1.9)	2 (2.7)
Aphasia	0	0	0	1 (1.9)	1 (1.4)
Dysarthria	0	0	0	1 (1.9)	1 (1.4)
Headache	0	0	0	1 (1.9)	1 (1.4)
Hypoesthesia	0	0	0	1 (1.9)	1 (1.4)
Lethargy	0	0	0	1 (1.9)	1 (1.4)
Sciatica	0	0	0	1 (1.9)	1 (1.4)
Spinal cord compression	0	0	0	1 (1.9)	1 (1.4)
VIIth nerve paralysis	0	0	1 (12.5)	0	1(1.4)
Respiratory, thoracic and mediastinal disorders -Total	0	0	0	4 (7.7)	4 (5.5)
Dyspnea	0	0	0	3 (5.8)	3 (4.1)
Hypoxia	0	0	0	1 (1.9)	1 (1.4)
Pleural effusion	0	0	0	1 (1.9)	1 (1.4)
Pneumothorax	0	0	0	1 (1.9)	1 (1.4)
Vascular disorders -Total	0	1 (14.3)	0	0	1 (1.4)
Hypotension	0	1 (14.3)	0	0	1 (1.4)

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Primary system organ class Preferred term	LFA102 10 mg/kg N=3 n (%)	LFA102 20 mg/kg N=7 n (%)	LFA102 40 mg/kg N=8 n (%)	LFA102 60 mg/kg N=52 n (%)	All Patients N=73 n (%)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the all patients column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 30(+2) days of the last study medication are reported.

Other Relevant Findings

Analysis of pharmacokinetics

Treatment	Statistics	AUC(0-tlast) (hr*ug/mL)	AUC(0-inf) (hr*ug/mL)	Cmax (ug/mL)	T1/2 (day)	Tmax (hr)	Tlast (hr)	Vz(mL)	Vss (mL)	CL (mL/day)
LFA102 3 mg/kg (N=3)	n	3	3	3	3	3	3	3	3	3
	Mean (SD)	11636.1 (3320.74)	11926.7 (3408.15)	85.9 (35.84)	5.602 (0.2365)	-	-	5194.951 (2307.7350)	4951.287 (1864.8079)	637.667 (261.1079)
	CV% mean	28.54	28.58	41.72	4.22	-	-	44.42	37.66	40.95
	Geo-mean	11337.6	11621.7	81.3	5.599	-	-	4849.920	4680.549	600.373
	CV% geo-mean	28.13	28.04	42.02	4.20	-	-	48.44	44.83	45.45
	Median	10619.8	10800.5	74.7	5.550	7.767	670.550	4899.808	5455.265	629.000
	[Min; Max]	[8942; 15346]	[9224; 15755]	[57; 126]	[5.40; 5.86]	[2.00; 8.03]	[670.23; 696.67]	[3048.99; 7636.06]	[2886.29; 6512.31]	[381.00; 903.00]
	(Q1,Q3)	[8942;15346]	[9224;15755]	[57; 126]	[5.40; 5.86]	[2.00; 8.03]	[670.23; 696.67]	[3048.99; 7636.06]	[2886.29; 6512.31]	[381.00; 903.00]
LFA102 10 mg/kg (N=3)	n	3	3	3	3	3	3	3	3	3
	Mean (SD)	44450.0 (6925.74)	47514.9 (9120.17)	303.0 (58.51)	7.129 (4.2539)	-	-	4116.800 (1266.0560)	3867.094 (573.1413)	444.667 (125.0013)
	CV% mean	15.58	19.19	19.31	59.67	-	-	30.75	14.82	28.11
	Geo-mean	44070.4	46890.3	299.2	6.403	-	-	3996.007	3837.586	432.649
	CV% geo-mean	16.37	20.50	19.83	59.25	-	-	30.07	15.42	29.57
	Median	46754.1	50518.7	304.0	4.901	4.000	673.483	3661.269	4007.880	444.000
	[Min; Max]	[36666 ; 49930]	[37272 ; 54754]	[244 ; 361]	[4.45 ; 12.03]	[2.40 ; 4.00]	[671.23 ; 717.75]	[3141.54 ; 5547.59]	[3236.68 ; 4356.72]	[320.00 ; 570.00]
	(Q1,Q3)	[36666 ; 49930]	[37272 ; 54754]	[244 ; 361]	[4.45 ; 12.03]	[2.40 ; 4.00]	[671.23 ; 717.75]	[3141.54 ; 5547.59]	[3236.68 ; 4356.72]	[320.00 ; 570.00]

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Treatment	Statistics	AUC(0-tlast) (hr*ug/mL)	AUC(0-inf) (hr*ug/mL)	Cmax (ug/mL)	T1/2 (day)	Tmax (hr)	Tlast (hr)	Vz(mL)	Vss (mL)	CL (mL/day)
LFA102 20 mg/kg(N=7)	n	6	5	7	6	7	7	5	5	5
	Mean (SD)	84349.1 (38746.82)	95036.9 (46016.51)	545.4 (115.91)	8.721 (2.5440)	-	-	5047.579 (2321.0545)	4246.120 (1852.3339)	449.400 (211.7942)
	CV% mean	45.94	48.42	21.25	29.17	-	-	45.98	43.62	47.13
	Geo-mean	75375.4	84413.0	534.9	8.355	-	-	4610.046	3948.767	409.481
	CV% geo-mean	59.82	62.51	21.60	34.71	-	-	52.31	44.46	51.90
	Median	90667.6	113094.3	527.0	9.431	3.917	669.933	4843.138	4138.196	348.000
	[Min; Max]	[32377; 128828]	[39998; 141260]	[377; 741]	[4.62; 11.77]	[1.02; 7.75]	[239.92; 672.78]	[2183.14; 8651.13]	[2223.20; 7243.19]	[217.00; 726.00]
	(Q1,Q3)	[45922; 117633]	[52106; 128727]	[485; 631]	[6.96; 10.11]	[2.02 ; 4.00]	[360.80; 671.33]	[4485.42; 5075.08]	[3450.30; 4175.72]	[342.00; 614.00]
LFA102 40 mg/kg(N=8)	n	7	4	8	7	8	8	4	4	4
	Mean (SD)	145779.0 (37900.78)	192490.5 (21146.22)	1092.4 (235.19)	8.886 (2.7093)	-	-	6277.300 (2561.2287)	5442.858 (1918.9665)	467.790 (155.6736)
	CV% mean	26.00	10.99	21.53	30.49	-	-	40.80	35.26	33.28
	Geo-mean	141291.9	191609.4	1072.5	8.524	-	-	5923.262	5187.749	450.275
	CV% geo-mean	28.17	11.13	20.18	32.38	-	-	40.18	37.29	31.99
	Median	148855.4	193217.2	1005.0	9.051	2.359	672.959	5653.839	5280.140	423.000
	[Min; Max]	[87506; 202336]	[167191; 216336]	[892; 1550]	[5.14; 13.28]	[2.00; 23.93]	[166.08; 676.17]	[3929.18; 9872.35]	[3388.52; 7822.64]	[339.00; 686.16]
	(Q1,Q3)	[122894; 172845]	[176146; 208835]	[924; 1220]	[6.92; 10.59]	[2.05; 4.13]	[503.28; 674.85]	[4550.61; 8003.99]	[3961.72; 6924.00]	[357.50; 578.08]
LFA102 60 mg/kg(N=52)	n	6	5	49	6	49	6	5	5	5
	Mean (SD)	230990.6 (102673.32)	286814.0 (101153.79)	1495.2 (589.27)	8.745 (0.9866)			7304.236 (2573.2177)	6763.701 (2529.7289)	587.868 (229.2374)
	CV% mean	44.45	35.27	39.41	11.28			35.23	37.40	38.99
	Geo-mean	210987.8	272294.9	1403.8	8.695			6802.138	6258.767	542.899

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Treatment	Statistics	AUC(0-tlast) (hr*ug/mL)	AUC(0-inf) (hr*ug/mL)	Cmax (ug/mL)	T1/2 (day)	Tmax (hr)	Tlast (hr)	Vz(mL)	Vss (mL)	CL (mL/day)
	CV% geo-mean	50.92	37.67	36.14	12.02			48.79	50.84	50.88
	Median	209931.1	255707.7	1410.0	8.895	2.067	670.750	8463.516	7708.862	591.000
	[Min; Max]	[101066; 359845]	[169860; 402726]	[648; 3970]	[6.96; 9.92]	[1.87; 4.00]	[384.50; 695.00]	[3069.34; 9630.20]	[2786.75; 9448.16]	[246.54; 852.00]
	(Q1,Q3)	[160515; 344655]	[224370; 381406]	[1160; 1790]	[8.63 ; 9.17]	[2.00; 2.17]	[668.75; 672.92]	[6808.29; 8549.82]	[6036.81; 7837.92]	[522.00; 727.80]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Conclusion:

- LFA102 was well tolerated and has an acceptable safety profile. No deaths or serious adverse events were suspected to be study drug related.
- There was no anti-tumor activity in terms of objective response of LFA102 observed both in the castration-resistant prostate cancer and metastatic breast cancer patients.
- The pharmacokinetics parameters Cmax and AUC(0-Tlast) increased in a relatively proportional manner with increasing LFA102 dose across 3 to 60 mg/kg doses.
- The geo-mean Vss and clearance across the treatment groups were similar across all the dose groups suggestive of the linear pharmacokinetics of LFA102.

Date of Clinical Trial Report

02 September 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

9 November 2014

Date of Latest Update

Reason for Update