Clinical trial results:
A Phase 2, Open-Label, Single-Arm, Multi-Center Study of AL101 in Patients With Adenoid Cystic Carcinoma (ACC) Bearing Activating Notch Mutations

Summary

EudraCT number	2019-000309-64
Trial protocol	GB FR NL
Global end of trial date	15 July 2022

Results information

Result version number	v1 (current)
This version publication date	16 February 2024
First version publication date	16 February 2024

Trial information

Trial identification

Sponsor protocol code	AL-ACC-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03691207
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ayala Pharmaceuticals, Inc.
Sponsor organisation address	Oppenheimer 4, Rehovot, Israel, 7670104
Public contact	Clinical Trial Information, Ayala Pharmaceuticals, Inc., ClinicalTrials.gov_Accuracy@ayalapharma.com
Scientific contact	Clinical Trial Information, Ayala Pharmaceuticals, Inc., ClinicalTrials.gov_Accuracy@ayalapharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical activity of AL101 using radiographic assessments and RECIST v1.1 in ACC patients with activating Notch mutations

Protection of trial subjects:

1. Drug-related (certain, probable/likely, possible) non-hematological Grade 3 and hematological Grade 4 toxicities will lead to dose level reduction for AL101.
2. To reduce the risk of infusion reactions caused by Cremophor, premedication with H1- and H2-blockers (diphenhydramine and ranitidine or equivalents) or dexamethasone will be given.
3. Management of diarrhea by treatment with Loperamide, interrupting AL101 dosing, increasing fluid intake and, if applicable, consider stopping antihypertensive therapy and nonsteroidal anti-inflammatory drugs and treat with dexamethasone.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	87
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	62
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was conducted between Dec 2018 to July 2022 in 7 countries: Canada, Netherlands, USA, Israel, France, Spain and the UK.

Pre-assignment

Screening details:

The study includes 2 cohorts, ran in a sequential fashion: Cohort 1 – AL101 4 mg once weekly (QW) intravenously (IV). Cohort 2 – AL101 6 mg QW IV.
Prior to entering the study, to determine eligibility, potential candidates underwent pre-screening assessment and confirmation for the presence of activating Notch mutations.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AL101 4mg

Arm description:

AL101 4 mg once weekly (QW) intravenously (IV)

Arm type	Experimental
Investigational medicinal product name	AL101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AL101 4 mg once weekly (QW) intravenously (IV)

Arm title	AL101 6mg

Arm description:

AL101 6 mg once weekly (QW) intravenously (IV)

Arm type	Experimental
Investigational medicinal product name	AL101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AL101 6 mg once weekly (QW) intravenously (IV)

Number of subjects in period 1	AL101 4mg	AL101 6mg
Started	45	42
Completed	0	0
Not completed	45	42
Consent withdrawn by subject	2	8
Death	41	26
Lost to follow-up	1	1
Sponsor decision	1	7

Baseline characteristics

Reporting groups	
Reporting group title	AL101 4mg
Reporting group description: AL101 4 mg once weekly (QW) intravenously (IV)	
Reporting group title	AL101 6mg
Reporting group description: AL101 6 mg once weekly (QW) intravenously (IV)	

Reporting group values	AL101 4mg	AL101 6mg	Total
Number of subjects	45	42	87
Age categorical Units: Subjects			
Adults (18-64 years)	35	27	62
From 65-84 years	10	15	25
Age continuous Units: years			
median	50	59	
full range (min-max)	25 to 79	25 to 80	-
Gender categorical Units: Subjects			
Female	25	18	43
Male	20	24	44
Race Units: Subjects			
Asian	2	1	3
Black or African American	4	2	6
White	31	33	64
Unknown or Not Reported	8	6	14

End points

End points reporting groups	
Reporting group title	AL101 4mg
Reporting group description: AL101 4 mg once weekly (QW) intravenously (IV)	
Reporting group title	AL101 6mg
Reporting group description: AL101 6 mg once weekly (QW) intravenously (IV)	

Primary: Overall Response Rate (ORR)	
End point title	Overall Response Rate (ORR)
End point description: ORR is defined as partial response (PR) + complete response (CR) as assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 for target lesions assessed by MRI. Complete Response (CR): Disappearance of all target lesions. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	
End point type	Primary
End point timeframe: 3 years and 7 months	

End point values	AL101 4mg	AL101 6mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: Participants	3	2		

Statistical analyses

Statistical analysis title	Statistical Analysis of Efficacy Outcomes
Comparison groups	AL101 4mg v AL101 6mg
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 1-sided

Secondary: Clinical Benefit Response Rate (CBR)	
End point title	Clinical Benefit Response Rate (CBR)
End point description: linical benefit response rate (CBR) is defined as complete response (CR) + partial response (PR) +	

stable disease (SD) by investigator review based on RECIST v1.1 for target lesions assessed by MRI.
Complete Response (CR): Disappearance of all target lesions.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Stable Disease (SD): Neither sufficient shrinkage (at least 30%) to qualify for PR nor sufficient increase (more than 20%) to qualify for PD, taking as reference the smallest sum diameters.

End point type	Secondary

End point timeframe:

3 years and 7 months

End point values	AL101 4mg	AL101 6mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: Participants	28	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined at the time from first infusion of investigational product to death due to any cause. Subjects with no documentation of death were censored at the last known date known to be alive.

End point type	Secondary

End point timeframe:

3 years and 5 months

End point values	AL101 4mg	AL101 6mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	36		
Units: month				
median (confidence interval 95%)	9.3 (6.6 to 14.2)	9.4 (5.9 to 11.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years and 7 months

Adverse event reporting additional description:

The analysis was done on the safety population which consists of 87 patients (45 patients in the 4mg arm, and 42 patients in the 6mg arm).
Safety analysis set includes all subjects who receive at least one infusion of study drug, including partial infusions.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	AL101 4mg

Reporting group description:

AL101 4 mg once weekly (QW) intravenously (IV)

Reporting group title	AL101 6mg

Reporting group description:

AL101 6 mg once weekly (QW) intravenously (IV)

Serious adverse events	AL101 4mg	AL101 6mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 45 (51.11%)	26 / 42 (61.90%)	
number of deaths (all causes)	41	26	
number of deaths resulting from adverse events	5	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain cancer metastatic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to central nervous system			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bronchial obstruction			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilic pneumonia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 45 (2.22%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 45 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 45 (4.44%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow infiltration			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 45 (0.00%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ileus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter sepsis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis orbital			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 45 (2.22%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 45 (8.89%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	2 / 5	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 45 (4.44%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 45 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AL101 4mg	AL101 6mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 45 (100.00%)	42 / 42 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 45 (15.56%)	4 / 42 (9.52%)	
occurrences (all)	21	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 45 (4.44%)	7 / 42 (16.67%)	
occurrences (all)	2	14	
Chills			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Facial pain			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	30 / 45 (66.67%)	25 / 42 (59.52%)	
occurrences (all)	44	35	
Mucosal inflammation			

subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	1	6	
Oedema peripheral			
subjects affected / exposed	1 / 45 (2.22%)	3 / 42 (7.14%)	
occurrences (all)	1	4	
Pyrexia			
subjects affected / exposed	3 / 45 (6.67%)	3 / 42 (7.14%)	
occurrences (all)	3	4	
Swelling face			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 45 (46.67%)	16 / 42 (38.10%)	
occurrences (all)	36	30	
Dysphonia			
subjects affected / exposed	8 / 45 (17.78%)	5 / 42 (11.90%)	
occurrences (all)	8	5	
Dyspnoea			
subjects affected / exposed	7 / 45 (15.56%)	8 / 42 (19.05%)	
occurrences (all)	7	9	
Epistaxis			
subjects affected / exposed	14 / 45 (31.11%)	14 / 42 (33.33%)	
occurrences (all)	19	25	
Hypoxia			
subjects affected / exposed	1 / 45 (2.22%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Nasal congestion			
subjects affected / exposed	4 / 45 (8.89%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Oropharyngeal pain			
subjects affected / exposed	4 / 45 (8.89%)	5 / 42 (11.90%)	
occurrences (all)	4	8	
Productive cough			

subjects affected / exposed	7 / 45 (15.56%)	4 / 42 (9.52%)	
occurrences (all)	9	4	
Nasal dryness			
subjects affected / exposed	3 / 45 (6.67%)	2 / 42 (4.76%)	
occurrences (all)	3	2	
Upper-airway cough syndrome			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 45 (6.67%)	2 / 42 (4.76%)	
occurrences (all)	3	2	
Depression			
subjects affected / exposed	3 / 45 (6.67%)	2 / 42 (4.76%)	
occurrences (all)	4	2	
Insomnia			
subjects affected / exposed	10 / 45 (22.22%)	11 / 42 (26.19%)	
occurrences (all)	10	12	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 45 (8.89%)	4 / 42 (9.52%)	
occurrences (all)	6	10	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 45 (8.89%)	3 / 42 (7.14%)	
occurrences (all)	4	7	
Weight decreased			
subjects affected / exposed	7 / 45 (15.56%)	11 / 42 (26.19%)	
occurrences (all)	7	14	
Neutrophil count increased			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Platelet count decreased			
subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	2	7	
Injury, poisoning and procedural complications			

Infusion related reaction			
subjects affected / exposed	4 / 45 (8.89%)	3 / 42 (7.14%)	
occurrences (all)	4	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 45 (13.33%)	4 / 42 (9.52%)	
occurrences (all)	6	4	
Dysgeusia			
subjects affected / exposed	7 / 45 (15.56%)	9 / 42 (21.43%)	
occurrences (all)	9	13	
Headache			
subjects affected / exposed	13 / 45 (28.89%)	4 / 42 (9.52%)	
occurrences (all)	19	5	
Neuralgia			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Taste disorder			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	7 / 45 (15.56%)	4 / 42 (9.52%)	
occurrences (all)	16	4	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Photophobia			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Vision blurred			
subjects affected / exposed	8 / 45 (17.78%)	3 / 42 (7.14%)	
occurrences (all)	8	3	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	5 / 45 (11.11%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Abdominal pain upper			
subjects affected / exposed	2 / 45 (4.44%)	3 / 42 (7.14%)	
occurrences (all)	4	3	
Constipation			
subjects affected / exposed	10 / 45 (22.22%)	10 / 42 (23.81%)	
occurrences (all)	12	12	
Diarrhoea			
subjects affected / exposed	31 / 45 (68.89%)	33 / 42 (78.57%)	
occurrences (all)	46	76	
Dry mouth			
subjects affected / exposed	7 / 45 (15.56%)	13 / 42 (30.95%)	
occurrences (all)	7	14	
Dyspepsia			
subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	1	5	
Dysphagia			
subjects affected / exposed	3 / 45 (6.67%)	3 / 42 (7.14%)	
occurrences (all)	3	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 45 (11.11%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Nausea			
subjects affected / exposed	30 / 45 (66.67%)	19 / 42 (45.24%)	
occurrences (all)	50	33	
Oral pain			
subjects affected / exposed	3 / 45 (6.67%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Stomatitis			
subjects affected / exposed	3 / 45 (6.67%)	7 / 42 (16.67%)	
occurrences (all)	4	8	
Vomiting			
subjects affected / exposed	21 / 45 (46.67%)	13 / 42 (30.95%)	
occurrences (all)	30	25	

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	9 / 45 (20.00%)	7 / 42 (16.67%)	
occurrences (all)	9	8	
Pruritus			
subjects affected / exposed	7 / 45 (15.56%)	5 / 42 (11.90%)	
occurrences (all)	9	5	
Alopecia			
subjects affected / exposed	8 / 45 (17.78%)	7 / 42 (16.67%)	
occurrences (all)	8	7	
Dermatitis acneiform			
subjects affected / exposed	4 / 45 (8.89%)	8 / 42 (19.05%)	
occurrences (all)	8	14	
Erythema			
subjects affected / exposed	1 / 45 (2.22%)	3 / 42 (7.14%)	
occurrences (all)	1	5	
Hair colour changes			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Night sweats			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 45 (6.67%)	3 / 42 (7.14%)	
occurrences (all)	5	7	
Rash			
subjects affected / exposed	8 / 45 (17.78%)	7 / 42 (16.67%)	
occurrences (all)	16	9	
Rash maculo-papular			
subjects affected / exposed	9 / 45 (20.00%)	7 / 42 (16.67%)	
occurrences (all)	18	18	
Skin lesion			
subjects affected / exposed	6 / 45 (13.33%)	2 / 42 (4.76%)	
occurrences (all)	7	3	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 45 (8.89%)	3 / 42 (7.14%)	
occurrences (all)	6	4	
Back pain			
subjects affected / exposed	13 / 45 (28.89%)	4 / 42 (9.52%)	
occurrences (all)	14	7	
Musculoskeletal pain			
subjects affected / exposed	3 / 45 (6.67%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	4 / 45 (8.89%)	0 / 42 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 45 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Oral candidiasis			
subjects affected / exposed	1 / 45 (2.22%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Pneumonia			
subjects affected / exposed	4 / 45 (8.89%)	4 / 42 (9.52%)	
occurrences (all)	4	6	
Rash pustular			
subjects affected / exposed	5 / 45 (11.11%)	0 / 42 (0.00%)	
occurrences (all)	5	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 45 (6.67%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)	3 / 42 (7.14%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 45 (20.00%)	11 / 42 (26.19%)	
occurrences (all)	9	15	
Hyperglycaemia			

subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Hypocalcaemia			
subjects affected / exposed	4 / 45 (8.89%)	5 / 42 (11.90%)	
occurrences (all)	10	6	
Hypokalaemia			
subjects affected / exposed	8 / 45 (17.78%)	6 / 42 (14.29%)	
occurrences (all)	11	6	
Hypomagnesaemia			
subjects affected / exposed	5 / 45 (11.11%)	0 / 42 (0.00%)	
occurrences (all)	6	0	
Hypophosphataemia			
subjects affected / exposed	25 / 45 (55.56%)	18 / 42 (42.86%)	
occurrences (all)	34	29	
Dehydration			
subjects affected / exposed	1 / 45 (2.22%)	4 / 42 (9.52%)	
occurrences (all)	1	5	
Hyponatraemia			
subjects affected / exposed	4 / 45 (8.89%)	1 / 42 (2.38%)	
occurrences (all)	8	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2019	1. Changes: Add prescreening procedures for NGS evaluation, and clarify biopsy requirements for archival and fresh tumor tissue. Clarify the procedure for confirmation of response. Shorten recruitment duration to 18 months. Rationale: Requested by sites to ensure only patients with activating Notch mutation will proceed into screening. 2. Changes: Safety laboratories to be done locally Rationale: Requested by sites, to allow faster review of data by investigator 3. Changes: Add and modify laboratory tests to be done during the study. Rationale: To enhance safety monitoring and align with the AL101 investigator's brochure. 4. Changes: Align dose modifications for hematological Grade 4 toxicities with AL101 Investigator's Brochure. Correct dose reduction instruction Rationale: To enhance safety monitoring, and alignment with the AL101 investigator's brochure and to ensure accuracy. 5. Changes: Update tissue archival collection to within 3 years and specify the number of unstained slides required (25). Rationale: To ensure tissue is viable for study purposes.
20 December 2019	1. Changes: Change primary endpoint to be Investigator assessed. Rationale: Investigator-assessed is appropriate for this study phase. Radiological images are being collected for central review should this become required. 2. Add objective/endpoint for patient reported outcome measure (EORTC QLQ-C30) to Cohort 2. Rationale: To evaluate the effect of AL101 6 mg QW on patients' quality of life. 3. Add sequential Cohort 2 (6 mg once weekly; QW) and clarify enrollment process. Rationale: Study expansion and higher dose (while adhering to set safety toxicity management guidelines), may improve efficacy and maintain patient's safety. The current results in patients with ACC suggest that a higher dose of AL101 may be well tolerated in this patient population particularly with the use of steroids and other toxicity management guidelines. Prior studies suggest that the increase to 6 mg will result in a higher exposure and more substantial inhibition of the Notch pathway and this may result in improved efficacy in this difficult to treat patient population. 4. Add dose reduction guidelines and toxicity management for Cohort 2 (6 mg QW). Rationale: To ensure safety.
27 August 2020	1. Delete exclusion criterion 9 - Patients treated with a nucleoside analogue within 6 months prior to administration of investigational product. Rationale: Based on data reanalysis, excluding nucleoside analogues is not supported with clinical or nonclinical data 2. Update exclusion criterion 12f - creatinine clearance <60 mL/min (Calculation of CrCl will be based on acceptable institution standard) Rationale: Allow inclusion based on normal creatinine values, as well as sufficient GFR, as AL101 is not expected to impact renal function 3. Introduce change in regimen (2 weeks on / 1 week off) for first episode of Grade 2 or 3 diarrhea and Grade 2 Colitis before dose reduction on subsequent episodes. Rationale: To allow investigators to use a 2 weeks on / 1 week off regimen at 6 mg QW, before implementing dose reduction. The aim is to introduce a scheduled dose interruption to prevent recurrence of toxicity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported